ESC European Society of Cardiology

European Heart Journal (2025) **00**, 1–102
https://doi.org/10.1093/eurheartj/ehaf194

ESC GUIDELINES

2025 ESC/EACTS Guidelines for the management of valvular heart disease

Developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

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Associations: Association for Acute CardioVascular Care (ACVC), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), and Heart Failure Association (HFA)

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SD All experts involved in the development of these guidelines have submitted declarations of interest, which are reported in a supplementary document to the guidelines. See the *European Heart Journal* online or https://www.escardio.org/Guidelines for supplementary documents as well as evidence tables.

Keywords Guidelines • European Society of Cardiology (ESC) • European Association for Cardio-Thoracic Surgery (EACTS) • Valvular heart disease • Aortic stenosis • Aortic regurgitation • Mitral stenosis • Mitral regurgitation • Tricuspid regurgitation • Tricuspid stenosis • Multivalvular disease • TAVI • SAVR • Heart surgery • Transcatheter edge-to-edge repair • Transcatheter valve replacement

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Abbreviations and acronyms

2D	Two-dimensional
3D	Three-dimensional
4D	Four-dimensional
ACE-I	Angiotensin-converting enzyme-inhibitor
ACTIVATION	PercutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION trial
AF	Atrial fibrillation
AO	Aorta
AP	Anteroposterior
AR	Aortic regurgitation
ARB	Angiotensin receptor blocker
AS	Aortic stenosis
ASA	Acetylsalicylic acid
ATLANTIS	Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis
AU	Agatston units
AV	Aortic valve
AVA	Aortic valve area
AVAi	Aortic valve area indexed for body surface area
AVATAR	Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis
AVCS	Aortic valve calcium score
AVr	Aortic valve repair
BASILICA	Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction
BAV	Bicuspid aortic valve
BHV	Biological heart valve
BNP	Brain natriuretic peptide
BP	Blood pressure
BSA	Body surface area
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCT	Cardiac computed tomography
CCTA	Coronary computed tomography angiography
CHA_2DS_2-VASc	Congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female)
CI	Confidence interval
CIED	Cardiac implantable electronic device
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CW	Continuous wave
CYP	Cytochrome P
DAPT	Dual antiplatelet therapy
DEDICATE	Randomized, Multicenter, Event-Driven Trial of TAVI versus SAVR in Patients with Symptomatic Severe Aortic-Valve Stenosis
DOAC	Direct oral anticoagulant
DSE	Dobutamine stress echocardiography
DVI	Doppler velocity index
EACTS	European Association for Cardio-Thoracic Surgery
EARLY TAVR	Evaluation of TAVR Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis trial
ECG	Electrocardiogram
EDV	End-diastolic velocity
ENVISAGE-TAVI AF	Edoxaban vs. Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation
EOA	Effective orifice area
EROA	Effective regurgitant orifice area
ESC	European Society of Cardiology
EuroSCORE	European System for Cardiac Operative Risk Evaluation
EVoLVeD	Early Valve Replacement guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe Aortic Stenosis
FAC	Fractional area change
FFR	Fractional flow reserve
FWS	Free wall strain
GALILEO	Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement (TAVR) to Optimize clinical outcomes trial
GDMT	Guideline-directed medical therapy
GLS	Global longitudinal strain
h	Hour
HALT	Hypo-attenuated leaflet thickening
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HTx	Heart transplantation
INR	International normalized ratio
IU	International unit
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrium/left atrial
LAAO	Left atrial appendage occlusion
LAAOS	Left Atrial Appendage Occlusion Study
LAMPOON	Laceration of the Anterior Mitral leaflet to Prevent Outflow ObstructioN
LAVI	Left atrial volume index
LMWH	Low-molecular-weight heparin
LV	Left ventricle/left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic diameter
LVESDi	Left ventricular end-systolic diameter indexed to BSA
LVESVi	Left ventricular end-systolic volume indexed to BSA
LVOT	Left ventricular outflow tract
MA	Mitral annulus

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MAC	Mitral annular calcification
MATTERHORN	Multicenter, Randomized, Controlled Study to Assess Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin trial
MHV	Mechanical heart valve
MITRA-FR	Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation trial
mPAP	Mean pulmonary artery pressure
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
MS	Mitral stenosis
M-TEER	Mitral transcatheter edge-to-edge repair
MV	Mitral valve
MVA	Mitral valve area
MVHD	Multiple valvular heart disease
N	No
NCS	Non-cardiac surgery
NOTION	Nordic Aortic Valve Intervention trial
NT-proBNP	N-terminal pro-B-type natriuretic protein
NYHA	New York Heart Association
OAC	Oral anticoagulation
PAWP	Pulmonary artery wedge pressure
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PH	Pulmonary hypertension
PHT	Pressure half-time
PISA	Proximal isovelocity surface area
P mean	Mean pressure gradient
PMC	Percutaneous mitral commissurotomy
PMR	Primary mitral regurgitation
POPular TAVI	Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation
PPM	Prosthesis–patient mismatch
PROM	Patient-reported outcome measure
PVL	Paravalvular leak
PVR	Pulmonary vascular resistance
RA	Right atrium/right atrial
RCT	Randomized controlled trial
RECOVERY	Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis
RESHAPE-HF2	Randomized Investigation of the MitraClip Device in Heart Failure: 2nd Trial in Patients with Clinically Significant Functional Mitral Regurgitation
RF	Regurgitant fraction
RHC	Right heart catheterization
RHD	Rheumatic heart disease
RV	Right ventricle/right ventricular
RVEF	Right ventricular ejection fraction
RVol	Regurgitant volume
SAM	Systolic anterior movement
SAPT	Single antiplatelet therapy
SAV	Surgical aortic valve
SAVR	Surgical aortic valve replacement
SGLT2i	Sodium–glucose co-transporter 2 inhibitor
SMR	Secondary mitral regurgitation
SPAP	Systolic pulmonary artery pressure
STS	Society of Thoracic Surgeons
STS-PROM	Society of Thoracic Surgeons predicted risk of mortality
SVD	Structural valve deterioration
SVi	Stroke volume index
TAPSE	Tricuspid annular plane systolic excursion
TAV	Transcatheter aortic valve
TAVI	Transcatheter aortic valve implantation
TDI	Tissue Doppler imaging
TEER	Transcatheter edge-to-edge repair
THV	Transcatheter heart valve
TMVI	Transcatheter mitral valve implantation
TOE	Transoesophageal echocardiography
TR	Tricuspid regurgitation
TRILUMINATE	Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System trial
TRISCEND	Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy using a Novel Device
TS	Tricuspid stenosis
TTE	Transthoracic echocardiography
TTR	Time in therapeutic range
TV	Tricuspid valve
UFH	Unfractionated heparin
VCA	Vena contracta area
VHD	Valvular heart disease
VKA	Vitamin K antagonist
V_{max}	Peak transvalvular velocity
VSARR	Valve-sparing aortic root replacement
VTE	Venous thromboembolism
VTI	Velocity time integral
WHO	World Health Organisation
WU	Wood unit
Y	Yes

1. Preamble

Guidelines evaluate and summarize available evidence with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. ESC/EACTS Guidelines are intended for use by health professionals but do not override their individual responsibility to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with the patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription and to respect the ethical rules of their profession.

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This guideline updates and replaces the previous version from 2021. This Task Force was selected by the ESC and the EACTS to include professionals

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Table 1 **Classes of recommendations**

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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Table 2 **Levels of evidence**

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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involved with the medical care of patients with this pathology and to include patient representatives and methodologists. The selection procedure included an open call for authors and aimed to include members from across the whole of the ESC region and from relevant ESC Subspecialty Communities. Consideration was given to diversity and inclusion.

Guidelines Task Forces perform a critical review and evaluation of the published literature on diagnostic and therapeutic approaches including assessment of the risk–benefit ratio. Recommendations are based on major randomized trials and relevant systematic reviews and meta-analyses, when available. Systematic literature searches are conducted in cases of controversy or uncertainty to ensure that all key studies were considered. For recommendations related to diagnosis and prognosis, additional types of evidence are included, such as diagnostic accuracy studies and studies focused on the development and validation of prognostic models. The strength of each recommendation and the level of evidence supporting it are weighed and scored according to pre-defined criteria as outlined in *Tables 1 and 2*. Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs) are also evaluated when available as the basis for recommendations and/or discussion in these guidelines.

Evidence tables summarizing key information from relevant studies are generated to facilitate the formulation of recommendations, to

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enhance comprehension of recommendations after publication, and to reinforce transparency in the guidelines development process. The tables are published in their own section of the guidelines and reference specific recommendation tables.

After an iterative process of deliberations, a first Task Force vote on all recommendations is conducted prior to the initiation of rounds of review. A second Task Force vote on all recommendations is conducted after the final round of review and revision. For each vote, the Task Force follows ESC voting procedures and all recommendations require at least 75% agreement among voting members to be approved. Voting restrictions may be applied based on declarations of interests.

The writing and reviewing panels provide declaration-of-interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest are reviewed according to the ESC declaration-of-interest rules, which can be found on the ESC website (http://www.escardio.org/doi) and are compiled in a report published in a supplementary document with the guidelines. Funding for the development of these ESC/EACTS Guidelines was derived entirely from the ESC and the EACTS with no involvement of the healthcare industry.

The ESC CPG Committee supervises and co-ordinates the preparation of new guidelines and approves their publication. In addition to review by the ESC CPG Committee, these ESC/EACTS Guidelines underwent multiple rounds of double-blind peer review on a dedicated online review platform. The review was conducted by topic experts, including members from ESC National Cardiac Societies, EACTS Network of National Cardiac Surgery Societies and from relevant ESC Subspecialty Communities. The Guideline Task Force considered all review comments and was required to respond to all those classified as major. After appropriate revisions, the Task Force, the ESC CPG Committee members and the EACTS Council members approved the final document for publication in the *European Heart Journal* and in the *European Journal of Cardio-Thoracic Surgery*.

Unless otherwise stated, the guideline content refers to sex, understood as the biological condition of being male or female, defined by genes, hormones, and sexual organs. Off-label use of medication may be presented in this guideline if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, decisions on off-label use must be made by the responsible health professional giving special consideration to ethical rules concerning healthcare, the specific situation of the patient, patient consent, and country-specific health regulations.

2. Introduction

New evidence has accumulated since the publication of the *2021 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines for the management of valvular heart disease*, leading to the need for new recommendations (*Table 3* New recommendations) and revision of existing recommendations (*Table 4* Revised recommendations) concerning the following topics:

- The importance of shared and patient-centred decision-making by multidisciplinary expert Heart Teams working within a regional network has been reinforced. Patients with complex conditions or requiring complex procedures should be referred to high-volume centres, where corresponding expertise is concentrated to ensure high-quality treatment.
- Advanced imaging modalities—such as three-dimensional (3D) echocardiography, cardiac computed tomography (CCT), and cardiac magnetic resonance (CMR) imaging—have gained importance and become a central aspect in the screening and evaluation of patients with valvular heart disease (VHD).
- Emphasis is put on the importance of correctly assessing the cause(s) and mechanism(s) of all valve diseases. In particular, the distinction between atrial and ventricular secondary mitral regurgitation (SMR) has clear implications in terms of prognosis and management.
- New evidence has been published regarding the benefits of intervention for the treatment of severe aortic stenosis (AS) irrespective of symptoms, left ventricular ejection fraction (LVEF), and flow reserve.
- The criteria used for decision-making concerning the optimal modality of AS treatment [transcatheter aortic valve (AV) implantation (TAVI) or surgical AV replacement (SAVR)] based on a Heart Team approach have been refined, including the combination of key aspects such as age, procedural risk, and anatomical suitability, incorporating estimated life expectancy and lifetime management considerations.
- Further randomized evidence confirming the mid-term safety and efficacy of TAVI in low-risk patients has been published.
- The indications for TAVI in patients with bicuspid AV (BAV) stenosis or severe aortic regurgitation (AR) at high surgical risk, based on anatomical suitability and a comprehensive Heart Team evaluation, are discussed.
- Several advancements have been made regarding the treatment of patients with primary mitral regurgitation (PMR): refinement of the criteria for intervention in asymptomatic patients; demonstration of the value of minimally invasive mitral valve (MV) surgery to reduce the length of hospital stay and accelerate recovery; and large-scale data confirming the role of transcatheter edge-to-edge repair (TEER) in high-risk patients.
- Longer-term follow-up data and two new randomized controlled trials (RCTs) concerning the management of patients with ventricular SMR have been published.
- The evidence for the treatment of tricuspid valve (TV) disease is growing—including new randomized data supporting concomitant TV repair during left-sided valve surgery, and transcatheter options (repair and replacement) that reduce tricuspid regurgitation (TR), promote reverse right ventricular (RV) remodelling, and improve quality of life compared with medical treatment.
- Efforts have been made to provide improved guidance regarding the diagnostic steps and management of patients with multiple and mixed VHD.
- Definitions of structural valve deterioration (SVD) have been updated and unified.
- The recommendations concerning the use of direct oral anticoagulants (DOACs) in patients with VHD have been updated, and the importance of education and (self-)monitoring is emphasized.
- Sex-specific considerations in patients with VHD have been extended and regrouped into a new dedicated section (see *Section 17*).

Because of demographic changes, patients with VHD frequently present with concomitant cardiovascular diseases, increasing the complexity of treatment strategies. These Guidelines focus on acquired

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VHD and do not deal in detail with overlapping cardiovascular diseases such as infective endocarditis,[5] chronic coronary syndrome,[6] and atrial fibrillation (AF),[7] as well as all scenarios of aortic or congenital disease,[8,9] because these topics are covered in separate Guidelines.

The *2025 ESC/EACTS Guidelines for the management of valvular heart disease* aim to be concise, focused on relevant issues for clinicians and patients, and to provide clear and simple practical recommendations, assisting healthcare providers in their daily clinical decision-making. A compilation of the evidence considered for new recommendations, or those with an updated class of recommendation or level of evidence, can be consulted online (see Supplementary data online, *Evidence Tables*). The Task Force for these Guidelines acknowledges that multiple factors influence and ultimately determine the most appropriate treatment of individual patients within a given community. These factors include the availability of equipment and technology, and the expertise and volumes, in complex procedures, such as valve repair or transcatheter interventions. Moreover, given the lack of evidence on some topics related to VHD, several recommendations are the result of expert consensus opinion. Therefore, deviations from these Guidelines may be appropriate in certain clinical circumstances, and decision-making should always be based on a collaborative, multidisciplinary Heart Team approach centred on individual characteristics, needs, and prognosis, as well as the preferences of the informed patient.

2.1. What is new

Table 3 New recommendations

Recommendations	Class[a]	Level[b]
Diagnosis of coronary artery disease—*Section 6.1*		
Omission of invasive coronary angiography should be considered in TAVI candidates, if procedural planning CT angiography is of sufficient quality to rule out significant CAD.	IIa	B
PCI should be considered in patients with a primary indication to undergo TAVI and ≥90% coronary artery stenosis in segments with a reference diameter ≥2.5 mm.	IIa	B
Indications for intervention in severe aortic regurgitation—*Section 7.4*		
TAVI may be considered for the treatment of severe AR in symptomatic patients ineligible for surgery according to the Heart Team, if the anatomy is suitable.	IIb	B
Indications for intervention in symptomatic and asymptomatic severe aortic stenosis, and recommended mode of intervention—*Section 8.5*		
Intervention should be considered in asymptomatic patients (confirmed by a normal exercise test, if feasible) with severe, high-gradient AS and LVEF ≥50%, as an alternative to close active surveillance, if the procedural risk is low.	IIa	A
TAVI may be considered for the treatment of severe BAV stenosis in patients at increased surgical risk, if the anatomy is suitable.	IIb	B
Indications for intervention in severe primary mitral regurgitation—*Section 9.1*		
Surgical MV repair is recommended in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) when a durable result is likely, if at least three of the following criteria are fulfilled: • AF • SPAP at rest >50 mmHg • LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm) • Concomitant secondary TR ≥ moderate.	I	B
Minimally invasive MV surgery may be considered at experienced centres to reduce the length of stay and accelerate recovery.	IIb	B
Indications for intervention in secondary mitral regurgitation—*Section 9.2*		
MV surgery, surgical AF ablation, if indicated, and LAAO should be considered in symptomatic patients with severe atrial SMR under optimal medical therapy.	IIa	B
TEER may be considered in symptomatic patients with severe atrial SMR not eligible for surgery after optimization of medical therapy including rhythm control, when appropriate.	IIb	B
MV surgery may be considered in patients with moderate SMR undergoing CABG.	IIb	B
Indications for mitral valve surgery and transcatheter intervention in clinically severe rheumatic and degenerative mitral stenosis—*Section 10.3*		
TMVI may be considered in symptomatic patients with extensive MAC and severe MV dysfunction at experienced Heart Valve Centres with expertise in complex MV surgery and transcatheter interventions.	IIb	C

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Indications for intervention in tricuspid regurgitation—*Section 11.4*		
Careful evaluation of TR aetiology, stage of the disease (i.e. degree of TR severity, RV and LV dysfunction, and PH), patient operative risk, and likelihood of recovery by a multidisciplinary Heart Team is recommended in patients with severe TR prior to intervention.	I	C
Surgery of concomitant severe mitral regurgitation—*Section 13.3*		
MV surgery is recommended in patients with severe MR undergoing surgery for another valve.	I	C
Indications for intervention in patients with mixed moderate aortic stenosis and moderate aortic regurgitation—*Section 13.3*		
Intervention is recommended in symptomatic patients with mixed moderate AV stenosis and moderate regurgitation, and a mean gradient ≥40 mmHg or V_{max} ≥4.0 m/s.	I	B
Intervention is recommended in asymptomatic patients with mixed moderate AV stenosis and moderate regurgitation, with V_{max} ≥4.0 m/s and LVEF <50% not attributable to other cardiac disease.	I	C
Prosthetic valve selection—*Section 14.1*		
An MHV should be considered in patients with an estimated long life expectancy, if there are no contraindications for long-term OAC.	IIa	B
Management of antithrombotic therapy in patients with a mechanical heart valve—*Section 14.3*		
It is recommended that INR targets are based on the type and position of MHV, patient's risk factors, and comorbidities.	I	A
Patient education is recommended to improve the quality of OAC.	I	A
Management of antithrombotic therapy in patients with mechanical heart valves undergoing elective non-cardiac surgery or invasive procedures—*Section 14.3*		
Continuing VKA treatment is recommended in patients with an MHV for minor or minimally invasive interventions associated with no or minimal bleeding.	I	A
Interruption (3–4 days before surgery), and resumption of VKA without bridging, may be considered to reduce bleeding in patients with new-generation aortic MHV and no other thromboembolic risk factors undergoing major non-cardiac surgery or invasive procedures.	IIb	B
Management of antithrombotic therapy in patients with a biological heart valve or valve repair—*Section 14.3*		
Surgical biological heart valve without indication for oral anticoagulation		
Lifelong low-dose ASA (75–100 mg/day) may be considered 3 months after surgical implantation of an aortic or mitral BHV in patients without clear indication for OAC.	IIb	C
Transcatheter aortic valve implantation without indication for oral anticoagulation		
DAPT is not recommended to prevent thrombosis after TAVI, unless there is a clear indication.	III	B
Surgical repair without indication for oral anticoagulation		
Low-dose ASA (75–100 mg/day) may be considered after surgical MV or TV repair in preference to OAC in patients without clear indication for OAC and at high bleeding risk.	IIb	B
Surgical biological heart valve with indication for oral anticoagulation		
OAC continuation is recommended in patients with a clear indication for OAC undergoing surgical BHV implantation.	I	B
DOAC continuation may be considered after surgical BHV implantation in patients with an indication for DOAC.	IIb	B
Surgical repair with indication for oral anticoagulation and/or antiplatelet therapy		
Continuation of OAC or antiplatelet therapy should be considered after surgical valve repair in patients with a clear indication for an antithrombotic therapy.	IIa	B
Management of mechanical heart valve failure—*Section 14.4*		
Reoperation is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Management of valve thrombosis—*Section 14.4*		
TOE and/or 4D-CT are recommended in patients with suspected valve thrombosis to confirm the diagnosis.	I	C

4D, four-dimensional; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; ASA, acetylsalicylic acid; AV, aortic valve; BAV, bicuspid aortic valve; BHV, biological heart valve; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CT, computed tomography; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; INR, international normalized ratio; LA, left atrium/left atrial; LAAO, left atrial appendage occlusion; LAVI, left atrial volume index; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to body surface area; MAC, mitral annular calcification; MHV, mechanical heart valve; MR, mitral regurgitation; MV, mitral valve; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PH, pulmonary hypertension; PMR, primary mitral regurgitation; RV, right ventricle/right ventricular; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary artery pressure; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair; TMVI, transcatheter mitral valve implantation; TOE, transoesophageal echocardiography; TR, tricuspid regurgitation; TV, tricuspid valve; VKA, vitamin K antagonist; V_{max}, peak transvalvular velocity.
[a]Class of recommendation.
[b]Level of evidence.

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Table 4 Revised recommendations

Recommendations in 2021 version	Class[a]	Level[b]	Recommendations in 2025 version	Class[a]	Level[b]
Management of coronary artery disease in patients with valvular heart disease—*Section 6.1*					
CCTA should be considered as an alternative to coronary angiography before valve surgery in patients with severe VHD and low probability of CAD.	IIa	C	CCTA is recommended before valve intervention in patients with moderate or lower (≤50%) pre-test likelihood of obstructive CAD.	I	B
Coronary angiography is recommended before valve surgery in patients with severe VHD and any of the following: • History of cardiovascular disease • Suspected myocardial ischaemia • LV systolic dysfunction • In men >40 years of age and post-menopausal women • One or more cardiovascular risk factors.	I	C	Invasive coronary angiography is recommended before valve intervention in patients with high and very high (>50%) pre-test likelihood of obstructive CAD.	I	C
Coronary angiography is recommended in the evaluation of severe SMR.	I	C	Invasive coronary angiography is recommended in the evaluation of CAD in patients with severe ventricular SMR.	I	C
PCI should be considered in patients with a primary indication to undergo TAVI and coronary artery diameter stenosis >70% in proximal segments.	IIa	C	PCI may be considered in patients with a primary indication to undergo transcatheter valve interventions and coronary artery stenosis ≥70% in proximal segments of main vessels.	IIb	B
PCI should be considered in patients with a primary indication to undergo transcatheter MV intervention and coronary artery diameter stenosis >70% in proximal segments.	IIa	C			
Management of atrial fibrillation in patients with native valvular heart disease—*Section 6.2*					
LAAO should be considered to reduce the thromboembolic risk in patients with AF and a CHA_2DS_2-VASc score ≥2 undergoing valve surgery.	IIa	B	Surgical closure of the LA appendage is recommended as an adjunct to OAC in patients with AF undergoing valve surgery to prevent cardioembolic stroke and systemic thromboembolism.	I	B
Concomitant AF ablation should be considered in patients undergoing valve surgery, balancing the benefits of freedom from atrial arrhythmias and the risk factors for recurrence (LA dilatation, years in AF, age, renal dysfunction, and other cardiovascular risk factors).	IIa	A	Concomitant surgical ablation is recommended in patients undergoing MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.	I	A
			Concomitant surgical ablation should be considered in patients undergoing non-MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.	IIa	B
The use of DOACs is not recommended in patients with AF and moderate-to-severe MS.	III	C	The use of DOACs is not recommended in patients with AF and rheumatic MS with an MVA ≤2.0 cm^2.	III	B
Indications for surgery in severe aortic regurgitation—*Section 7.4*					
AV repair may be considered in selected patients at experienced centres when durable results are expected.	IIb	C	AV repair should be considered in selected patients with severe AR at experienced centres, when durable results are expected.	IIa	B
Surgery may be considered in asymptomatic patients with LVESD >20 mm/m^2 BSA (especially in patients with small body size) or resting LVEF ≤55%, if surgery is at low risk.	IIb	C	AV surgery may be considered in asymptomatic patients with severe AR and LVESDi >22 mm/m^2 or LVESVi >45 mL/m^2 [especially in patients with small body size (BSA <1.68 m^2)], or resting LVEF ≤55%, if surgical risk is low.	IIb	B
Indications for intervention in symptomatic severe aortic stenosis—*Section 8.4.1*					
Intervention is recommended in symptomatic patients with severe low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with reduced LVEF (<50%), and evidence of flow (contractile) reserve.	I	B	Intervention is recommended in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with reduced LVEF (<50%) after careful confirmation that AS is severe.	I	B

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Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) AS with normal LVEF after careful confirmation that the AS is severe.	IIa	C	Intervention should be considered in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with normal LVEF (≥50%) after careful confirmation that AS is severe.	IIa	B
Indications for intervention in asymptomatic severe aortic stenosis—*Section 8.5*					
Intervention should be considered in asymptomatic patients with severe AS and LV dysfunction (LVEF <55%) without another cause.	IIa	B	Intervention should be considered in asymptomatic patients with severe AS and LVEF ≥50%, if the procedural risk is low and one of the following parameters is present: • Very severe AS (mean gradient ≥60 mmHg or V_{max} >5.0 m/s). • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year. • Markedly elevated BNP/NT-proBNP levels (more than three times age- and sex-corrected normal range, confirmed on repeated measurement without other explanation). • LVEF <55% without another cause.	IIa	B
Intervention should be considered in asymptomatic patients with LVEF >55% and a normal exercise test if the procedural risk is low and one of the following parameters is present: • Very severe AS (mean gradient ≥60 mmHg or V_{max} >5 m/s). • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year. • Markedly elevated BNP levels (more than three times age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation.	IIa	B			
Mode of intervention in symptomatic severe aortic stenosis—*Section 8.5*					
The choice between surgical and transcatheter intervention must be based upon careful evaluation of clinical, anatomical, and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice.	I	C	It is recommended that the mode of intervention is based on Heart Team assessment of individual clinical, anatomical, and procedural characteristics, incorporating lifetime management considerations and estimated life expectancy.	I	C
TAVI is recommended in older patients (≥75 years), or in those who are high risk (STS-PROM/EuroSCORE II >8%) or unsuitable for surgery.	I	A	TAVI is recommended in patients ≥70 years of age with tricuspid AV stenosis, if the anatomy is suitable.	I	A
SAVR is recommended in younger patients who are low risk for surgery (<75 years and STS-PROM/EuroSCORE II <4%), or in patients who are operable and unsuitable for transfemoral TAVI.	I	B	SAVR is recommended in patients <70 years of age, if the surgical risk is low.	I	B
SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical, and procedural characteristics.	I	B	SAVR or TAVI are recommended for all remaining candidates for an aortic BHV according to Heart Team assessment.[1–4]	I	B
Non-transfemoral TAVI may be considered in patients who are inoperable and unsuitable for transfemoral TAVI.	IIb	C	Non-transfemoral TAVI should be considered in patients who are unsuitable for surgery and transfemoral access.	IIa	B
Indications for intervention in severe primary mitral regurgitation—*Section 9.1.4*					
Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <40 mm and LVEF >60%) and AF secondary to MR or PH (SPAP at rest >50 mmHg).	IIa	B	MV surgery should be considered in asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) in the presence of PH (SPAP at rest >50 mmHg), or AF secondary to MR.	IIa	B
Surgical MV repair should be considered in low-risk asymptomatic patients with LVEF >60%, LVESD <40 mm, and significant LA dilatation (volume index ≥60 mL/m^2 or diameter ≥55 mm) when performed in a Heart Valve Centre and a durable repair is likely.	IIa	B	Surgical MV repair should be considered in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) in the presence of significant LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm), when performed in a Heart Valve Centre and a durable repair is likely.	IIa	B

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TEER may be considered in symptomatic patients who fulfil the echocardiographic criteria of eligibility, are judged inoperable or at high surgical risk by the Heart Team, and for whom the procedure is not considered futile.	IIb	B	TEER should be considered in symptomatic patients with severe PMR who are anatomically suitable and at high surgical risk according to the Heart Team.	IIa	B
Severe ventricular secondary mitral regurgitation and concomitant coronary artery disease—*Section 9.2*					
In symptomatic patients who are judged not appropriate for surgery by the Heart Team on the basis of their individual characteristics, PCI (and/or TAVI) possibly followed by TEER (in case of persisting severe SMR) should be considered.	IIa	C	PCI followed by TEER after re-evaluation of MR may be considered in symptomatic patients with chronic severe ventricular SMR and non-complex CAD.	IIb	C
Indications for intervention in severe ventricular secondary mitral regurgitation without concomitant coronary artery disease—*Section 9.2*					
TEER should be considered in selected symptomatic patients not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment.	IIa	B	TEER is recommended to reduce HF hospitalizations and improve quality of life in haemodynamically stable, symptomatic patients with impaired LVEF (<50%) and persistent severe ventricular SMR, despite optimized GDMT and CRT (if indicated), fulfilling specific clinical and echocardiographic criteria.	I	A
In high-risk symptomatic patients not eligible for surgery and not fulfilling the criteria suggesting an increased chance of responding to TEER, the Heart Team may consider in selected cases a TEER procedure or other transcatheter valve therapy if applicable, after careful evaluation for ventricular assist device or heart transplant.	IIb	C	TEER may be considered for symptom improvement in selected symptomatic patients with severe ventricular SMR not fulfilling the specific clinical and echocardiographic criteria, after careful evaluation of LVAD or HTx.	IIb	B
Valve surgery may be considered in symptomatic patients judged appropriate for surgery by the Heart Team.	IIb	C	MV surgery may be considered in symptomatic patients with severe ventricular SMR without advanced HF who are not suitable for TEER.	IIb	C
Indications for intervention in tricuspid regurgitation in patients with left-sided valvular heart disease requiring surgery—*Section 11.4*					
Surgery is recommended in patients with severe primary TR undergoing left- sided valve surgery.	I	C	Concomitant TV surgery is recommended in patients with severe primary or secondary TR.	I	B
Surgery is recommended in patients with severe secondary TR undergoing left-sided valve surgery.	I	B			
Surgery should be considered in patients with moderate primary TR undergoing left-sided valve surgery.	IIa	C	Concomitant TV repair should be considered in patients with moderate primary or secondary TR, to avoid progression of TR and RV remodelling.	IIa	B
Surgery should be considered in patients with mild or moderate secondary TR with a dilated annulus (≥40 mm or >21 mm/m^2 by 2D echocardiography) undergoing left-sided valve surgery.	IIa	B	Concomitant TV repair may be considered in selected patients with mild secondary TR and tricuspid annulus dilatation (≥40 mm or >21 mm/m^2) to avoid progression of TR and RV remodelling.	IIb	B
Indications for intervention in patients with severe tricuspid regurgitation without left-sided valvular heart disease requiring surgery—*Section 11.4*					
Transcatheter treatment of symptomatic secondary severe TR may be considered in inoperable patients at a Heart Valve Centre with expertise in the treatment of TV disease.	IIb	C	Transcatheter TV treatment should be considered to improve quality of life and RV remodelling in high-risk patients, with symptomatic severe TR despite optimal medical therapy, in the absence of severe RV dysfunction or pre-capillary PH.	IIa	A
Prosthetic valve selection—*Section 14.1*					
A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to the high risk for thromboembolism.	IIb	C	An MHV may be considered in patients with a clear indication for long-term OAC.	IIb	C
Management of antithrombotic therapy in patients with a mechanical heart valve—*Section 14.3*					
OAC using a VKA is recommended lifelong for all patients with an MHV prosthesis.	I	B	Lifelong OAC with a VKA is recommended for all patients with MHVs to prevent thromboembolic complications.	I	A

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For patients with a VKA, INR self-management is recommended provided appropriate training and quality control are performed.	I	B	INR self-monitoring and self-management are recommended over standard monitoring in selected, trained patients to improve efficacy.	I	A
In patients with MHVs, it is recommended to (re)initiate the VKA on the first post-operative day.	I	C	Following cardiac surgery with MHV implantation, it is recommended to start UFH or LMWH bridging and VKA within 24 h, or as soon as considered safe.	I	B
In patients who have undergone valve surgery with an indication for post-operative therapeutic bridging, it is recommended to start either UFH or LMWH 12–24 h after surgery.	I	C			
The addition of low-dose ASA (75–100 mg/day) to VKA may be considered in selected patients with MHVs in case of concomitant atherosclerotic disease and low risk of bleeding.	IIb	C	The addition of low-dose ASA (75–100 mg/day) to VKA should be considered in selected patients with MHVs in case of concomitant symptomatic atherosclerotic disease, considering the individual bleeding risk profile.	IIa	B
The addition of low-dose ASA (75–100 mg/day) to VKA should be considered after thromboembolism despite an adequate INR.	IIa	C	Either an increase in INR target or the addition of low-dose ASA (75–100 mg/day) should be considered in patients with MHVs who develop a major thromboembolic complication despite documented adequate INR.	IIa	C
DOACs are not recommended in patients with an MHV prosthesis.	III	B	DOACs and/or DAPT are not recommended to prevent thrombosis in patients with an MHV.	III	A
Management of antithrombotic therapy in patients with mechanical heart valves undergoing elective non-cardiac surgery or invasive procedures—*Section 14.3*					
It is recommended that VKAs are timely discontinued prior to elective surgery to aim for an INR <1.5.	I	C	It is recommended to discontinue VKA at least 4 days before major elective non-cardiac surgery, aiming for an INR <1.5, and to resume VKA treatment within 24 h after surgery, or as soon as considered safe.	I	B
In patients with MHVs, it is recommended to (re)initiate the VKA on the first post-operative day.	I	C			
Therapeutic doses of either UFH or subcutaneous LMWH are recommended for bridging.	I	B	VKA interruption and resumption with bridging should be considered in patients with an MHV and thromboembolic risk factors undergoing major non-cardiac surgery.	IIa	B
Bridging of OAC, when interruption is needed, is recommended in patients with any of the following indications: • MHV • AF with significant MS • AF with CHA_2DS_2-VASc score ≥3 for women or 2 for men • Acute thrombotic event within the previous 4 weeks • High acute thromboembolic risk.	I	C			
Management of antithrombotic therapy in patients with a biological heart valve or valve repair—*Section 14.3*					
Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.	I	A	Low-dose ASA (75–100 mg/day) is recommended for 12 months after TAVI in patients without indication for OAC.	I	A
			Long-term (after the first 12 months) low-dose ASA (75–100 mg/day) should be considered after TAVI in patients without clear indication for OAC.	IIa	C
OAC is recommended lifelong for TAVI patients who have other indications for OAC.	I	B	OAC is recommended for TAVI patients who have other indications for OAC.	I	B
OAC with VKA should be considered during the first 3 months after mitral and tricuspid repair.	IIa	C	OAC, with either VKAs or DOACs, should be considered during the first 3 months after surgical MV or TV repair.	IIa	B
Routine use of OAC is not recommended after TAVI in patients without baseline indication.	III	B	Routine use of OAC is not recommended after TAVI in patients without baseline indication.	III	A
Management of haemolysis and paravalvular leak—*Section 14.4*					
Decision on transcatheter or surgical closure of clinically significant PVLs should be considered based on patient risk status, leak morphology, and local expertise.	IIa	C	It is recommended that the decision between transcatheter or surgical closure of clinically significant PVLs is based on Heart Team evaluation, including patient risk, leak morphology, and local expertise.	I	C

Continued

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Transcatheter closure should be considered for suitable PVLs with clinically significant regurgitation and/or haemolysis in patients at high or prohibitive surgical risk.	IIa	B	Transcatheter closure should be considered for suitable PVLs with clinically significant regurgitation and/or haemolysis.	IIa	B
Management of biological heart valve failure—*Section 14.4*					
Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient (after exclusion of valve thrombosis) or severe regurgitation.	I	C	Reintervention is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Transcatheter, transfemoral valve-in-valve implantation in the aortic position should be considered by the Heart Team depending on anatomical considerations, features of the prosthesis, and in patients who are at high operative risk or inoperable.	IIa	B	Transcatheter transfemoral valve-in-valve implantation in the aortic position should be considered in patients with significant valve dysfunction who are at intermediate or high surgical risk, and have suitable anatomical and prosthesis features, as assessed by the Heart Team.	IIa	B
Transcatheter valve-in-valve implantation in the mitral and tricuspid position may be considered in selected patients at high risk for surgical reintervention.	IIb	B	Transcatheter transvenous mitral or tricuspid valve-in-valve implantation should be considered in patients with significant valve dysfunction at intermediate or high surgical risk, if the anatomy is suitable.	IIa	B
Management of mechanical heart valve thrombosis—*Section 14.4*					
Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious comorbidity.	I	B	Heart Team evaluation is recommended in patients with acute HF (NYHA class III or IV) due to obstructive MHV thrombosis to determine appropriate management (repeat valve replacement or low-dose slow infusion fibrinolysis).	I	B
Fibrinolysis (using recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 min with UFH or streptokinase 1 500 000 U in 60 min without UFH) should be considered when surgery is not available or is very high risk, or for thrombosis of right-sided prostheses.	IIa	B			
Management of biological heart valve thrombosis—*Section 14.4*					
Anticoagulation using a VKA and/or UFH is recommended in BHV thrombosis before considering reintervention.	I	C	OAC using VKA is recommended in BHV thrombosis before considering reintervention.	I	B

2D, two-dimensional; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; ASA, acetylsalicylic acid; AV, aortic valve; BHV, biological heart valve; BNP, brain natriuretic peptide; BSA, body surface area; CAD, coronary artery disease; CCT, cardiac computed tomography; CCTA, coronary computed tomography angiography; CHA_2DS_2-VASc, congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female); CRT, cardiac resynchronization therapy; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GDMT, guideline-directed medical therapy; h, hour; HF, heart failure; HTx, heart transplantation; INR, international normalized ratio; LA, left atrium/left atrial; LAAO, left atrial appendage occlusion; LAVI, left atrial volume index; LMWH, low-molecular-weight heparin; LV, left ventricle/left ventricular; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to BSA; LVESVi, left ventricular end-systolic volume indexed to BSA; MHV, mechanical heart valve; min, minute; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PH, pulmonary hypertension; PMR, primary mitral regurgitation; PVL, paravalvular leak; RV, right ventricle/right ventricular; SAPT, single antiplatelet therapy; SAVR, surgical aortic valve replacement; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary artery pressure; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; SVi, stroke volume index; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation; TV, tricuspid valve; UFH, unfractionated heparin; VHD, valvular heart disease; VKA, vitamin K antagonist; V_{max}, peak transvalvular velocity.
[a]Class of recommendation.
[b]Level of evidence.

3. The Heart Team and Heart Valve Centre

3.1. The Heart Valve Network

Despite increasing attention within the medical community, VHD continues to be underdiagnosed and undertreated in the general population, and public awareness remains low.[10–13] Beside screening using auscultation and imaging when appropriate, the co-ordinated implementation of Heart Teams, Heart Valve Centres, and Heart Valve Networks at a local level represents an essential step to timely diagnose and treat patients with VHD.

An integrated regional Heart Valve Network, incorporating outpatient Heart Valve Clinics (for initial diagnosis and ongoing surveillance) and specialist Heart Valve Centres (for advanced imaging and surgical or transcatheter intervention), allows optimal patient care through timely access to specialist assessment, accurate diagnosis, improved decision-making, and matching of patients to healthcare providers with appropriate expertise, experience, and resources (*Figure 1*).[12] In addition, dedicated Heart Valve Clinics ensure consistent application of clinical guidelines, efficient use of resources, and overall high-quality patient care, which in turn may improve outcomes.[14,15] Medical goals include careful clinical and echocardiographic evaluation, monitoring at appropriate time intervals (so-called 'watchful waiting'), application

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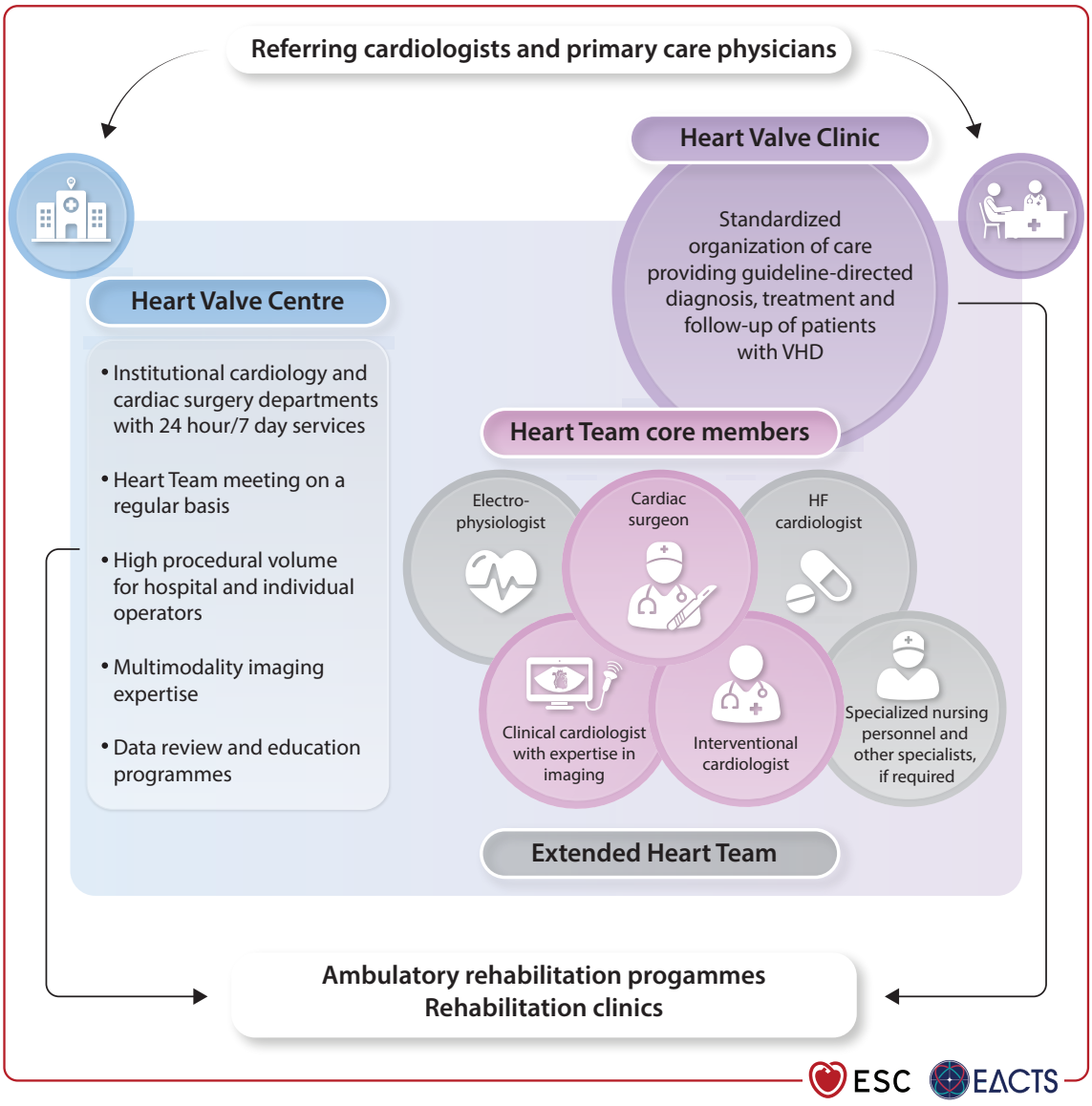
Referring cardiologists and primary care physicians
Heart Valve Clinic
Standardized organization of care providing guideline-directed diagnosis, treatment and follow-up of patients with VHD
Heart Valve Centre
• Institutional cardiology and cardiac surgery departments with 24 hour/7 day services
• Heart Team meeting on a regular basis
• High procedural volume for hospital and individual operators
• Multimodality imaging expertise
• Data review and education programmes
Heart Team core members
Electro-physiologist
Cardiac surgeon
HF cardiologist
Clinical cardiologist with expertise in imaging
Interventional cardiologist
Specialized nursing personnel and other specialists, if required
Extended Heart Team
Ambulatory rehabilitation progammes
Rehabilitation clinics
ESC
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Figure 1 The Heart Valve Network. HF, heart failure; VHD, valvular heart disease.

of guideline-directed medical therapy (GDMT), timely referral, and post-procedural follow-up.[15,16] Broader aims include patient education, the training of physicians and nurse specialists, swift and efficient access to specialist care, and recruitment into clinical trials.

Heart Valve Centres should ensure that their facilities match institutional and local statutory requirements (*Table 5*), report procedural volumes and outcomes, and monitor treatment quality. They hold responsibility for the training and education of surgeons, interventional and imaging cardiologists, dedicated nurses, and allied professionals.[17,18] Expertise in the surgical management of coronary artery disease (CAD), vascular diseases, and complications must be available. New techniques should be taught by trained mentors using simulator models, when feasible, to minimize learning-curve effects. More broadly, Heart Valve Centres co-ordinate the management of patients with VHD across the entire Heart Valve Network, supporting services at community level, encouraging early referral, and promoting education and communication with other medical departments, referring cardiologists, primary care physicians, and rehabilitation clinics.

3.1.1. Composition of the Heart Team

The Heart Team is now an established feature of VHD programmes that has been formally endorsed by previous ESC/EACTS Guidelines[19,20] and corresponding organizations worldwide.[17]

The value of the Heart Team approach has become increasingly apparent as options for the treatment of VHD have extended to include high-risk and inoperable patients (most of whom now undergo transcatheter interventions), and low-risk and asymptomatic patients (who derive prognostic benefit from increasingly safe procedures). Despite significant accumulation of data concerning the management of VHD over the last two decades, many patients in daily practice have clinical characteristics that do not match those of participants included in clinical trials. The Heart Team approach is therefore particularly helpful when there is uncertainty or a lack of strong evidence.

The Heart Team meeting facilitates balanced presentation of all appropriate options for medical, interventional, and surgical treatment, using tools and techniques for shared decision-making.

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The patient's preference plays a central role in this process, although the Heart Team recommendation should be based upon key objective medical considerations (particularly the relative risks and benefits of any procedure).

Meetings should take place on a regular basis with standardized minimum datasets (to ensure that all relevant information is available) and appropriate administrative support (often provided by specialist nurses with expertise in the care of patients with VHD). In-person meetings of the full Heart Team may not be feasible for every patient, and local standardized protocols may be implemented to facilitate swift decision-making for specific cohorts (e.g. elderly TAVI candidates or young patients with BAV disease). Equally, the need for Heart Team evaluation should not paralyse clinical decision-making, and *ad hoc* discussions remain appropriate in urgent situations.

Core members of the Heart Team include the cardiologist treating the patient (who is best placed to present their case and act as their advocate), specialists in advanced cardiovascular imaging and peri-procedural guiding,[21,22] surgeons, and interventional cardiologists with training and expertise in surgical and transcatheter valve procedures. Specialized nursing personnel play an essential role to improve patient information and education, as well as co-ordinate work-up and management steps in high-volume centres (*Figure 1*; *Table 5*). Cardiologists with expertise in heart failure (HF) and electrophysiology, as well as geriatricians, cardiovascular anaesthetists, and intensivists involved in peri-procedural care, should also be available to facilitate the discussion of particularly complex clinical scenarios when needed (extended Heart Team) (*Figure 1*; *Table 5*).

Table 5 Requirements for a Heart Valve Centre

Requirements
Centre performing heart valve procedures with on-site interventional cardiology and cardiac surgery departments providing 24-h/7-day services. **Heart Team core members:** Cardiologist with imaging expertise, interventional cardiologist, cardiac surgeon. **Additional specialists, if required (Extended Heart Team):** Specialized nursing personnel, HF specialist, electrophysiologist, cardiovascular anaesthetist, geriatrician, and other specialists (e.g. intensive care, vascular surgery, infectious diseases, neurology, radiology). The Heart Team must meet on a regular basis and work according to locally defined standard operating procedures and clinical governance arrangements. A hybrid cardiac catheterization laboratory is desirable. High volume for hospital and individual operators.
Multimodality imaging (including advanced echocardiography, CCT, CMR, and nuclear techniques) and expertise in peri-procedural imaging guidance of surgical and transcatheter procedures.
Heart Valve Clinic for outpatient assessment and follow-up.
Data review: continuous monitoring, evaluation, and reporting of procedural volumes and quality indicators, including clinical outcomes, as well as PROMs complemented by local/external audits. Education programmes targeting primary care and referring physicians, operators, and diagnostic and interventional imaging specialists.

CCT, cardiac computed tomography; CMR, cardiac magnetic resonance; HF, heart failure; PROM, patient-reported outcome measure.

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3.1.2. Procedural volume and clinical outcomes

The correlation between high institutional (and individual operator) volume and best procedural outcomes is intuitive, yet complex. Nevertheless, there is evidence of such a relationship for many cardiovascular procedures including SAVR,[23,24] surgical MV repair,[25,26] mitral and tricuspid TEER,[27–30] and TAVI (particularly in centres with an associated high-volume SAVR programme).[31–33] Studies have shown that an annualized operator volume of approximately 25 surgical mitral valve procedures,[26] 50 TAVIs (~100 per centre),[33] a cumulative experience of ~50 M-TEER procedures per operator/centre,[27] and a site volume of more than 20 T-TEERs/year[30] are associated with improved technical and clinical outcomes. Higher institutional surgical volume is associated with lower complication rates,[34–36] improved management,[37] and better infrastructural support.[38,39]

National procedural activity varies widely between high-, middle-, and low-income countries,[40] and it is therefore difficult to provide recommendations concerning the precise number of institutional or operator procedures that is required for high-quality care, excellent facilities, and processes. Instead, a network approach that highlights the importance of centres performing a high volume of procedures (e.g. based upon quartiles in individual countries or regions) seems more suitable, with complex procedures concentrated in the centres with the highest volumes (*Table 6*).

Table 6 Complex procedures ideally performed in the most experienced Heart Valve Centres

Transcatheter interventions	Surgical interventions
• Transfemoral TAVI in patients with high-risk features: – Low coronary ostia – Difficult femoral anatomy – Bicuspid valve – Severe calcification protruding into the LVOT – Severe LV and/or RV impairment – Pure AV regurgitation – Multiple valve disease – Complex coronary artery disease – Severe extracardiac disease (e.g. renal failure, PH) • Non-transfemoral TAVI • Valve-in-valve (including TAV-in-TAV) • All leaflet modification procedures (BASILICA, LAMPOON etc.) • PVL closure procedures • Complex M-TEER[a] • Redo M-TEER procedures • Tricuspid or mitral valve-in-ring or valve-in-valve, valve-in-MAC • TMVI • All tricuspid procedures	• High-risk procedures (especially in patients with LV and/or RV impairment) • Redo procedures • Minimally invasive and robotic valve surgery • Complex MV repair – Barlow disease – Anterior or bileaflet prolapse – High risk of SAM – Severe MAC • AV repair • Ross procedure • Valve surgery combined with complex surgery of the aorta • Endocarditis surgery

AV, aortic valve; BASILICA, Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction; LAMPOON, Laceration of the Anterior Mitral leaflet to Prevent Outflow ObstructioN; LV, left ventricular/left ventricle; LVOT, left ventricular outflow tract; MAC, mitral annular calcification; M-TEER, mitral transcatheter edge-to-edge repair; MV, mitral valve; PH, pulmonary hypertension; PVL: paravalvular leak; RV, right ventricular/right ventricle; SAM, systolic anterior movement; TAV, transcatheter aortic valve; TAVI, transcatheter aortic valve implantation; TMVI, transcatheter mitral valve implantation.
[a]See Supplementary Table S2.

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Internal quality assessment (see dedicated document concerning TAVI from the ESC[41]), systematic recording, and public availability of the volume and outcome data of the performed procedures are essential. Participation in national or international registries should be encouraged. These considerations are of particular importance regarding asymptomatic low-risk patients (where low mortality and procedural safety are paramount), those with multiple comorbidities (where the need for multidisciplinary collaboration is essential), and new techniques with a steep learning curve (where better results may be obtained at experienced centres).

There is a pressing need to ensure higher dispersion and adoption of interventions for VHD, especially (but not exclusively) in middle- and lower-income countries where rheumatic heart disease (RHD) remains the principal cause of VHD.[42,43] Key strategies include awareness programmes, increased public and medical education, simplified and improved diagnostic tools, and measures to reduce costs and facilitate access to evidence-based treatment options.[44]

4. Imaging of patients with valvular heart disease

Multimodality imaging is now the standard approach in VHD management to determine the pathophysiology, assess severity, plan interventions, and identify complications (*Figure 2*). The use of imaging for the assessment of each specific valve lesion is described in the corresponding sections. The role of imaging is transversal from diagnosis to follow-up and should encompass an integrative assessment.

4.1. Initial valve assessment

Comprehensive transthoracic echocardiography (TTE) is the first-line examination to confirm valve dysfunction, and determine the aetiology, mechanism, and severity of VHD, as well as cardiac chamber anatomy and damage.[45,46] It should be performed by properly trained imagers.[47–49] Quantitative imaging analysis (as opposed to visual) should be the goal in all patients with relevant VHD, complemented by qualitative and semi-quantitative evaluation. The severity of VHD should be assessed using an integrative approach of all criteria checked for consistency. When TTE is of poor quality or inconclusive, transoesophageal echocardiography (TOE) and/or additional diagnostic imaging modalities should be applied (e.g. calcium scoring and anatomy of the valve using CCT). In specific clinical scenarios [e.g. thrombosis, prosthetic valve dysfunction, endocarditis, mitral stenosis (MS), assessment of MV or TV anatomy], TOE has a central diagnostic role.[50,51]

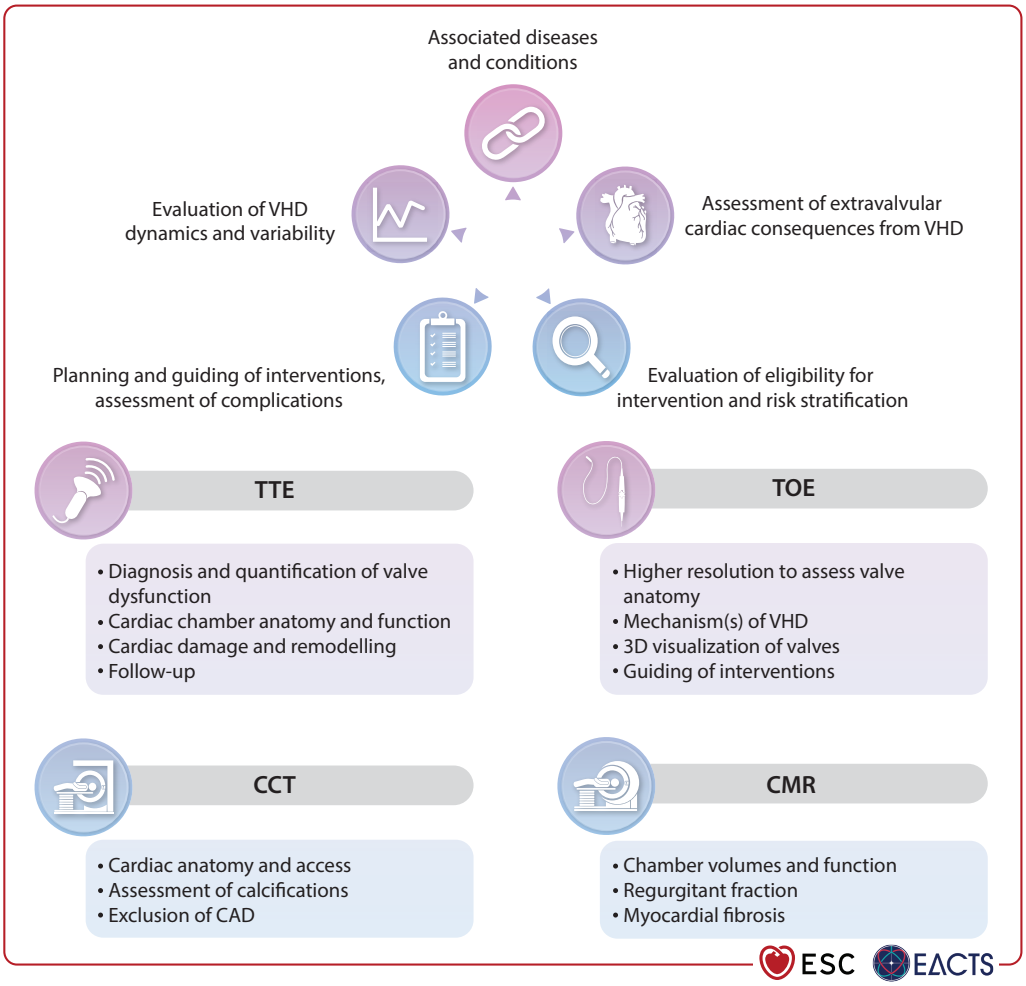
Associated diseases and conditions
Evaluation of VHD dynamics and variability
Assessment of extravalvular cardiac consequences from VHD
Planning and guiding of interventions, assessment of complications
Evaluation of eligibility for intervention and risk stratification
TTE
• Diagnosis and quantification of valve dysfunction
• Cardiac chamber anatomy and function
• Cardiac damage and remodelling
• Follow-up
TOE
• Higher resolution to assess valve anatomy
• Mechanism(s) of VHD
• 3D visualization of valves
• Guiding of interventions
CCT
• Cardiac anatomy and access
• Assessment of calcifications
• Exclusion of CAD
CMR
• Chamber volumes and function
• Regurgitant fraction
• Myocardial fibrosis
ESC
EACTS

Figure 2 Integrative imaging assessment of patients with valvular heart disease. 3D, three-dimensional; CAD, coronary artery disease; CCT, cardiac computed tomography; CMR: cardiac magnetic resonance; TOE; transoesophageal echocardiography; TTE, transthoracic echocardiography; VHD, valvular heart disease.

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Moreover, in patients with regurgitant lesions, particularly AR, CMR has gained key value in clinical practice.

4.2. Associated diseases and conditions

Imaging plays a crucial role in identifying associated diseases and conditions. The presence of concomitant left ventricular (LV) systolic or diastolic dysfunction, RV systolic dysfunction, red flags indicating cardiomyopathies (e.g. amyloidosis, hypertrophic cardiomyopathy), and aortopathy should prompt further examinations to ensure optimal risk stratification and VHD management. In addition to TTE, advanced imaging modalities, like CCT, may be required to assess the aorta, single-photon emission computed tomography (CT) for detection of ischaemia/necrosis, positron emission tomography (PET) for inflammation, nuclear scintigraphy for cardiac amyloidosis, or CMR for tissue characterization.

4.3. Evaluation of valvular heart disease dynamics and variability

Serial imaging studies to detect changes over time, or variability due to haemodynamic conditions or initiation/up-titration of medical therapy, are of utmost importance to guide decisions. The dynamic pattern of VHD may convey additional prognostic information. Exercise echocardiography helps to identify the cause of dyspnoea, unveil symptoms in apparently asymptomatic patients, identifies dynamic changes of VHD severity, and can contribute to refinement of the indication for an intervention, especially for AS and mitral regurgitation (MR).[52]

4.4. Assessment of extravalvular cardiac consequences from valvular heart disease

Several studies investigating different valve lesions have established the relevance of extravalvular cardiac damage in terms of prognosis,[53–55] recovery after intervention,[56] and quality of life.[57] The presence of LV hypertrophy, left atrium (LA) dilatation, LV or RV dysfunction and/or remodelling, myocardial fibrosis, and pulmonary hypertension (PH) provide important prognostic information, and may influence the timing and type of treatment. Although not necessarily chronological in their order of appearance, the understanding of cardiac damage, particularly damage involving the LV, is essential to guide appropriate medical therapy before and after any intervention. Transthoracic echocardiography (TTE) including global longitudinal strain (GLS) and CMR can be particularly useful in that regard.[58–60]

4.5. Evaluation of eligibility, planning, and guiding of interventions

Transoesophageal echocardiography (TOE) (preferentially 3D) is the preferred tool for the assessment of suitability for aortic, mitral, and TV repair.[45,49,61–63] Risk stratification for an intervention should integrate all the points mentioned above.

Transoesophageal echocardiography (TOE), including standard 3D views, is also the modality of choice to guide atrioventricular transcatheter interventions and should be performed by specially trained interventional echocardiographers.[61,64] Cardiac computed tomography (CCT) is frequently used to evaluate the relationship of the valve with adjacent structures [e.g. coronary arteries and left ventricular outflow tract (LVOT)], the extension of calcification [e.g. in mitral annular calcification (MAC)], and for sizing of the prosthesis. CT angiography is frequently employed to evaluate the anatomy of surgical, arterial, or venous access routes and detect cardiac or extracardiac complications (e.g. bleeding or embolic events). Coronary CT angiography (CCTA) is increasingly utilized to assess the presence of CAD.

5. Clinical evaluation of patients with valvular heart disease

5.1. Clinical examination

Patients with VHD can be either asymptomatic or present with a wide spectrum of symptoms, including acute or chronic HF. An initial meticulous history and a comprehensive physical examination of the patient with auscultation, documentation of clinical signs of HF such as dyspnoea, impaired physical capacity and fatigue, peripheral oedema, and pleural effusion, as well as a systematic frailty assessment, are crucial.[65] In addition, comorbidities and coexisting cardiac conditions should be documented (*Figure 3*). Particular attention should be given to recent changes in symptoms or physical findings indicating a potential worsening of the valve lesion or ventricular function.

5.2. Assessment of comorbidities and risk stratification

Risk stratification of patients with VHD has been mainly developed based on surgical populations. The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II)[66,67] (https://www.euroscore.org) and the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score[68] (http://riskcalc.sts.org/stswebriskcalc/calculate) are the most commonly used scoring systems to estimate surgical risk. Both risk scores have been calibrated to predict post-operative outcomes.[69–71] The STS-PROM score is dynamic to account for changes in patient risk profiles, the type of procedure (aortic, mitral, and tricuspid), and outcomes over time. The outdated (logistic) EuroSCORE I model systematically overestimated surgical mortality.[70,72]

In patients considered for TAVI, surgical risk scores have lower accuracy and tend to overestimate the risk of events.[73–75] Discrepancies between observed and predicted peri-procedural mortality after TAVI using surgical risk scores point towards a need for TAVI-specific scores. Models predicting short- and medium-term survival specifically designed for TAVI are rarely used in daily clinical practice due to limitations of their predictive performance.[76–79] Specific scores have also been developed for patients undergoing mitral TEER (M-TEER),[80–82] but the high heterogeneity of the population with MR limits their external validity and therefore routine clinical use so far.[83] Recently, a dedicated clinical score has been calibrated and validated to stratify the risk associated with first-time and repeat isolated TV surgery (TRI-SCORE; https://www.tri-score.com/), and its use should be encouraged for patients with TV disease,[84,85] as an alternative to the more complex Society of Thoracic Surgeons (STS) score for isolated TV surgery (https://isolatedtvsurgcalc.research.sts.org/).

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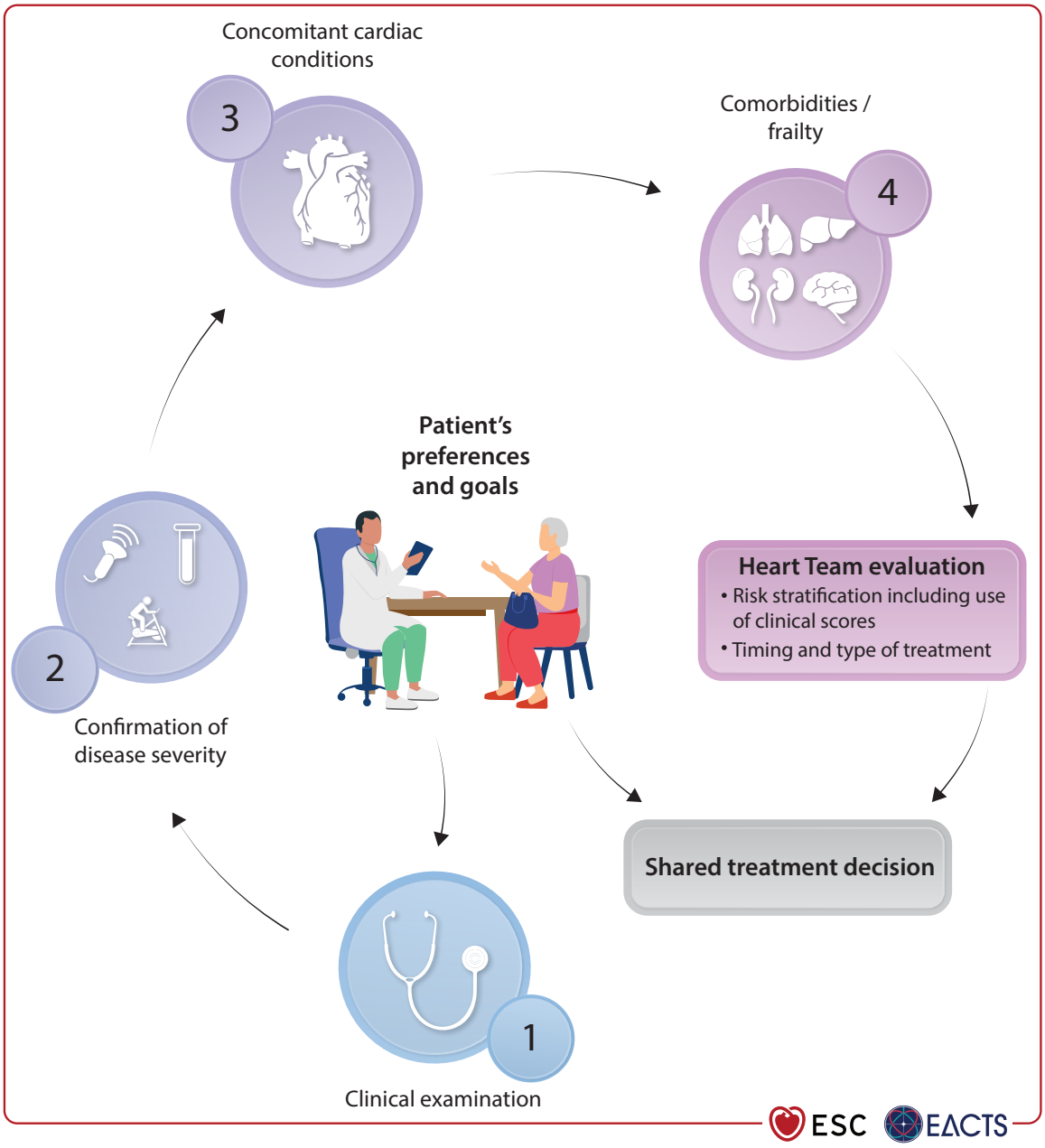

Figure 3 Central illustration. Patient-centred evaluation for treatment of valvular heart disease.

Other cardiac conditions and comorbidities—such as CAD, concomitant multiple valve and aortic disease, and RV dysfunction, as well as chronic kidney disease (CKD)—are not always appropriately captured in risk models, even if they are known to impact outcomes.[86] Similarly, specific unfavourable characteristics like porcelain aorta, mobile aortic atheroma, and previous mediastinal radiation therapy increase the surgical risk, and therefore may favour transcatheter treatment options. Frailty, including nutritional state, represents another important determinant of outcomes after valve interventions,[87–89a] which can be evaluated using appropriate tools as summarized in a recent consensus statement.[90] Several methods have been proposed, from the simple Fried Frailty Index to more complex scores[91] such as the Hospital Frailty Risk Score, which has been validated in a large cohort of TAVI and M-TEER patients.[92]

The use of PROMs that engage patients in the co-evaluation of their health and wellbeing is encouraged. Several scoring systems have been proposed and validated for reproducibility and association with clinical outcomes, like the Quality of Recovery 15-item PROM or the Kansas City Cardiomyopathy Questionnaire (KCCQ).[93–95]

5.3. Biomarkers

Biomarker levels indicating either cardiac wall stress [e.g. brain natriuretic peptide (BNP)] or myocardial damage (e.g. troponin), in asymptomatic and symptomatic patients, may help to monitor VHD progress and determine the most appropriate timing of intervention. In patients with VHD, the natriuretic peptide ratio [the ratio of measured BNP or N-terminal pro-B-type natriuretic protein

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(NT-proBNP) to upper limit of normal for age, sex, and assay] has been shown to be a powerful, independent, and incremental predictor of mortality.[96–98] In patients undergoing AV replacement, the accumulation of several elevated biomarkers of cardiovascular stress was associated with higher all-cause and cardiovascular mortality, and a higher rate of repeat hospitalization.[99,100]

5.4. Exercise testing

Because of the slow progression of valve lesions, patients may gradually limit their activity levels over several years and deny having actual symptoms that can be unmasked by exercise testing.[12] This is particularly important in cases of AS, because once symptoms occur there is a sharp increase in the risk of sudden cardiac death, unless a valve intervention is performed.[101–104] Exercise testing may provide additional information about the haemodynamic severity of VHD and help determine the risk and optimal timing of intervention by objectively evaluating functional capacity.[101,103] Cardiopulmonary exercise testing has a prognostic role and can assist decision-making in patients with VHD of intermediate severity, particularly those with asymptomatic AR.[101,105,106]

Exercise echocardiography is used for the assessment of LV global and segmental function, pulmonary artery pressure, and aortic and mitral pressure gradients.[101,107] It also documents exercise-induced increase of MR and TR severity, especially in patients with secondary disease.[108,109] Prognostic impact has been shown mainly for AS and MR.[110,111] Misconceptions regarding its risk and tolerability contribute to the overall underuse of exercise testing in patients with VHD,[12] despite data confirming its safety in most asymptomatic patients.[112,113]

5.5. Invasive investigations

5.5.1. Coronary angiography

Coronary artery assessment is recommended to evaluate the need for revascularization when valve surgery or an intervention is planned. The information regarding the existence of concomitant CAD should be available at the time of Heart Team discussion. CCTA is recommended as an alternative to coronary angiography to rule out CAD in patients who are at low or moderate risk of obstructive CAD.

Coronary blood flow and fractional flow reserve (FFR) are altered in the setting of concomitant VHD, and functional haemodynamic assessment of CAD in these patients is not well established.[114–118]

5.5.2. Cardiac catheterization

Right heart catheterization (RHC) should be performed in patients with equivocal echocardiographic findings, particularly those with MV disease, as well as in all candidates for the treatment of severe TR. In exceptional cases with unclear AS severity, it can be combined with measurements of the transaortic gradients allowing estimation of the aortic valve area (AVA). Right heart catheterization contributes to assess the repercussions of any left-sided VHD or LV impairment on the pulmonary circulation and right side of the heart. It provides information regarding volume state, cardiac output, and vascular resistance, differentiating between pre- and post-capillary PH, and should be ideally performed in euvolaemia.

Measurements of the pulmonary capillary wedge pressure v-wave can inform about MR severity, but are neither sensitive nor specific, and may also be increased if the compliance of the LA is reduced or in case of diastolic LV dysfunction, as in patients with MS or chronic HF.[119]

Similarly, the height of the right atrium (RA) v-wave, and the pressure curve mimicking the RV pattern ('ventricularization' of the RA pressure), are signs of relevant TR, which are frequently accompanied by increased RV end-diastolic pressure in case of associated RV dysfunction. In patients with severe TR, pulmonary vascular resistance (PVR) should be calculated to unmask pulmonary vascular disease, which may not be captured by echocardiography due to RV systolic dysfunction or underestimation of pulmonary pressures because of TR.

5.6. Patient-centred care and shared decision-making

Given that treatment of VHD typically involves several modalities and specialities, and may result in a complex and sometimes time-consuming decision-making process, patient education and information, using online material and face-to-face conversations, are essential at each step. A clearly defined point of contact for all questions relating to the disease or type of treatments should be communicated to the patient and their relatives.[120] The symptomatic and prognostic benefits, as well as the advantages and disadvantages of any treatment option, should be presented in an open and evidence-based manner. This includes mortality and risks of reintervention and complications (also over the long term), as well as recovery time and the need for cardiac, and if necessary psychological, rehabilitation until return to physical activity and work. Other issues to be discussed before the procedure include the need for oral anticoagulation (OAC) and its monitoring, as well as the noise generated by mechanical heart valves (MHVs). Information regarding centre experience and volume for a specific procedure should be provided. Misconceptions (e.g. subjective overestimation of the risk of surgery) should be addressed and potential interactions with individual lifestyle factors—including social activities, family and professional life, and hobbies—should be discussed in detail.

The Heart Team recommendation regarding the treatment and its modality must be based on evidence and anatomical considerations, balancing the risks and benefits of available treatment options.[16] The patient and patient's relatives need to be well informed about the rationale leading to the Heart Team recommendation, and given ample time to share personal preferences.[121] At the end of the process, a shared decision is made between the treating team and the informed patient and relatives (*Figure 3*).

6. Management of conditions associated with valvular heart disease

6.1. Diagnosis and management of coronary artery disease

The presence of CAD plays an important role in decision-making regarding the timing and modality of treatment, and should be assessed before Heart Team discussion. In patients with a low or moderate pre-test likelihood of obstructive CAD (≤50%), CCTA is recommended to rule out relevant CAD with high sensitivity.[122–124]

Several studies have investigated the value of CCT angiography for CAD screening in elderly TAVI candidates. While sensitivity for the detection of obstructive CAD is high (95%–97%), specificity (68%–73%) is

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modest, mainly explained by the high prevalence of coronary artery calcification and AF in patients with severe AS, which limit imaging resolution and interpretability.[125,126] If CCT angiography obtained during standard pre-TAVI evaluation is of sufficient quality to exclude relevant CAD, omission of invasive coronary angiography should be considered.[125–129]

The value of invasive functional haemodynamic assessment of CAD in patients with severe AS may be limited, because AS impacts coronary haemodynamics. Therefore, caution is warranted in the interpretation of functional measurements in the presence of severe AS until more data are available.[115,116]

Recommendations for the management of chronic CAD associated with VHD are provided below (*Recommendation Table 1*), as well as in dedicated guideline documents.[6] The indications for coronary artery bypass grafting (CABG) in patients undergoing surgery for the treatment of VHD are mainly based on observational data, which do not provide detailed information on the degree of stenosis and the complexity of CAD.[130] It has been demonstrated that subendocardial blood flow in the myocardium improves early after SAVR, most likely due to improved cardiac output and reduction of LV wall stress.[131] The presence of CAD is associated with peri-operative and late adverse events in patients with AS undergoing SAVR[132] that likely outweigh the increased risk of peri-procedural adverse events of combined SAVR and CABG compared with isolated SAVR. Indeed, in a large observational study, patients with CAD demonstrated better long-term survival after combined SAVR and CABG compared with SAVR alone, despite longer cross-clamp times.[133] In patients with a primary indication for valve surgery, CABG is recommended in patients with coronary artery stenosis of ≥70% and should be considered in those with stenosis of ≥50%–70%, given the opportunity of concomitant full revascularization.

The impact of CAD in patients undergoing TAVI remains under investigation. The randomized Nordic Aortic Valve Intervention (NOTION)-3 trial compared a strategy of routine percutaneous coronary intervention (PCI) versus conservative management in 455 patients with severe symptomatic AS undergoing TAVI, who also had stable CAD and at least one stenosis of ≥90% based on visual angiographic assessment or FFR of ≤0.80 in a segment with ≥2.5 mm reference diameter.[134] Percutaneous coronary intervention was associated with lower risk of a composite endpoint event including all-cause death, myocardial infarction or urgent revascularization at a median follow-up of 2 years. Exploratory analyses suggest that the increased risk in the conservative treatment arm was driven by differences in the risk of myocardial infarction and urgent revascularization in patients with a diameter stenosis of ≥90%, rather than those with positive FFR and stenosis of <90%. The risk of bleeding was higher in the PCI than in the conservative treatment group. Another multicentre RCT, the PercutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION (ACTIVATION) trial, was discontinued due to slow recruitment.[135] In this underpowered and thus inconclusive trial, a routine PCI strategy of ≥70% stenoses in main epicardial vessels (or ≥50% if protected left main or vein graft) did not meet non-inferiority compared with conservative CAD treatment with respect to the composite of all-cause death and rehospitalization; moreover, PCI was associated with higher bleeding rates. Observational data show that TAVI can be performed safely in patients with untreated CAD with low short- and long-term rates of acute coronary syndrome and unplanned coronary revascularization.[135–139] In two recent meta-analyses of mostly observational data, PCI was not associated with a mortality benefit in patients with chronic CAD undergoing TAVI.[140,141]

Optimal timing of PCI in patients undergoing TAVI remains yet to be determined. In NOTION-3, PCI was performed before TAVI in the majority of the patients (concomitantly or shortly after in only 26% of the patients). Decision-making concerning the timing of PCI should take into account the type of valve used for TAVI and the complexity of the coronary lesions.[142,143] Valves with a high frame—particularly in the context of a narrow aortic root, commissural misalignment, or valve-in-valve procedures—can pose challenges for coronary access following TAVI.[144,145] The presence of significant CAD should therefore be considered for optimal transcatheter valve selection and reinforces the importance of optimized implantation technique and commissural alignment.[143,146] Several RCTs comparing the value and timing of PCI with medical therapy are ongoing (NCT04634240, NCT04310046, and NCT05078619).

Based on the available data, PCI should be considered in patients with a primary indication to undergo TAVI and high-grade (≥90%) coronary artery stenosis in large vessels of ≥2.5 mm. In patients with stenosis of ≥70%, PCI may be considered based on symptom status.[142,143] In patients with ischaemic ventricular SMR, surgical revascularization of CAD has been associated with MR reduction[147] and favourable clinical outcomes in observational studies.[148,149] According to very limited data, improvement of SMR may occur in a minority of patients (about one-third) after PCI, which may therefore be considered prior to MV intervention.[150]

For patients with VHD presenting with acute coronary syndrome, treatment decisions should be made according to the most recent ESC Guidelines.[151] In patients presenting with non-ST-segment elevation acute coronary syndrome, it may be particularly challenging to determine the leading cause of elevated troponin levels, which are also frequently observed in decompensated VHD. Therefore, the treatment strategy should be determined by the Heart Team, taking into account symptoms, as well as coronary, valve, and access anatomy.[136,138,139]

Recommendation Table 1 — Recommendations for the management of chronic coronary syndrome in patients with valvular heart disease (see also Supplementary data online, *Evidence Table 1*)

Recommendations	Class[a]	Level[b]
Diagnosis of coronary artery disease		
CCTA is recommended before valve intervention in patients with moderate or lower (≤50%) pre-test likelihood of obstructive CAD.[122–124]	I	B
Invasive coronary angiography is recommended before valve intervention in patients with high and very high (>50%) pre-test likelihood of obstructive CAD.	I	C
Invasive coronary angiography is recommended in the evaluation of CAD in patients with severe ventricular SMR.	I	C
Omission of invasive coronary angiography should be considered in TAVI candidates, if procedural planning CT angiography is of sufficient quality to rule out significant CAD.[125–129]	IIa	B

Continued

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Indications for myocardial revascularization		
CABG is recommended in patients with a primary indication for valve surgery and coronary artery stenosis ≥70%.[c]	I	C
CABG should be considered in patients with a primary indication for valve surgery and coronary artery stenosis ≥50%–70%.	IIa	C
PCI should be considered in patients with a primary indication to undergo TAVI and ≥90% coronary artery stenosis in segments with a reference diameter ≥2.5 mm.[134]	IIa	B
PCI may be considered in patients with a primary indication to undergo transcatheter valve interventions and coronary artery stenosis ≥70% in proximal segments of main vessels.[135–137]	IIb	B

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CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CT, computed tomography; PCI, percutaneous coronary intervention; SMR, secondary mitral regurgitation; TAVI, transcatheter aortic valve implantation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Stenosis ≥50% can be considered for left main stenosis.

6.2. Atrial fibrillation

The interplay between AF and VHD is complex, and has an essential role in the prognosis and evolution of VHD during the patient's lifetime. Valvular heart disease is independently associated with AF and almost one-third of patients with AF have a history of VHD.[152] Conversely, AF is the main trigger of the development of atrial secondary MR and TR. In a recent cohort study, 8% of individuals with AF developed moderate or severe TR within 3 years of follow-up compared with only 2% in those in sinus rhythm.[153] While disturbed annular dynamics have been postulated,[150,154] the exact pathophysiology leading to secondary atrioventricular VHD in some, but not all patients with AF remains largely unclear.

Detailed recommendations on the anticoagulation management of patients with VHD and AF are provided below (*Recommendation Table 2*) and in *Section 14*, as well as in specific Guidelines.[7] Patients with a combination of VHD and AF have a high incidence of thromboembolic or bleeding complications.[155] DOACs have replaced vitamin K antagonists (VKAs) in most clinical scenarios and are recommended for patients with VHD presenting with AF, except for patients with a MHV or mitral stenosis with a valve area ≤2.0 cm^2. The use of apixaban,[156] dabigatran,[157] edoxaban,[158] and rivaroxaban[159] is supported by subgroup analyses of large RCTs. Recommendations regarding the antithrombotic treatment of patients with MHVs and biological heart valves (BHVs) are described in *Section 14* of these Guidelines.

In the Left Atrial Appendage Occlusion Study (LAAOS) III trial, surgical left atrial appendage occlusion (LAAO) in patients with AF and a CHA_2DS_2-VASc [congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female)] score of ≥2 points undergoing cardiac surgery was associated with a 33% reduction of the risk of stroke or systemic embolism at a mean follow-up of 3.8 years.[160] These findings were confirmed by a large meta-analysis including four RCTs.[161] A subanalysis of LAAOS III showed that the benefit of LAAO remains consistent irrespective of the use of VKAs or DOACs, as well as in the absence of OAC (although representing only 10% of the included population).[162] In an RCT including patients with severe AS and AF undergoing TAVI, concomitant transcatheter LAAO was non-inferior to medical therapy with respect to a composite primary endpoint including all-cause mortality, stroke, and major bleeding at 2 years. Of note, rates of major or life-threatening bleeding were similar in the two groups and arterial or venous thromboembolisms more frequent in the TAVI/LAAO arm, leaving uncertainty regarding the usefulness of combining both procedures.[163]

Recommendation Table 2 — Recommendations for the management of atrial fibrillation in patients with native valvular heart disease (see also Supplementary data online, *Evidence Tables 2 and 3*)

Recommendations	Class[a]	Level[b]
Anticoagulation		
DOACs are recommended for stroke prevention in preference to VKAs in patients with AF and AS, AR, or MR who are eligible for OAC.[156–159,164]	I	A
The use of DOACs is not recommended in patients with AF and rheumatic MS with an MVA ≤2.0 cm^2.[165]	III	B
Surgical interventions		
Concomitant surgical ablation is recommended in patients undergoing MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.[166–173]	I	A
Surgical closure of the LA appendage is recommended as an adjunct to OAC in patients with AF undergoing valve surgery to prevent cardioembolic stroke and systemic thromboembolism.[160–162]	I	B
Concomitant surgical ablation should be considered in patients undergoing non-MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.[167,169,174,175]	IIa	B

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AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; DOAC, direct oral anticoagulant; LA, left atrium/left atrial; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; OAC, oral anticoagulation; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

6.3. Cancer and radiation therapy

Valvular heart disease is commonly associated with cancer and represents a well-known long-term side effect of intensive radiation therapy[176] for treatment of Hodgkin or non-Hodgkin lymphoma, breast cancer, and other thoracic malignancies.[177] Clinically significant VHD most commonly appears decades after radiotherapy. The incidence of radiation-induced VHD is increasing owing to longer survival of patients with cancer. Risk factors are summarized in Supplementary data online, *Table S1*. Patients at risk should be screened for VHD using TTE 10 years after radiation exposure and followed up every 5 years thereafter.[178]

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Radiotherapy may lead to aortic and/or valvular calcification, CAD of proximal segments, restrictive cardiomyopathy, pericardial adhesions and calcifications with constriction, restrictive lung disease, chest wall scarring, and impaired wound healing, especially in patients who underwent radiation by means of older techniques (>20 years ago). The above factors complicate any surgical approach and increase the operative risk, which is underestimated by traditional risk scores.[179–181] TAVI is proposed as an alternative for patients presenting with radiation-induced AS in the *2022 ESC Guidelines on cardio-oncology*[182] based on favourable, but limited, observational data,[183,184] because this category of patients has been excluded from RCTs.[183,184] Furthermore, M-TEER in patients presenting with radiation-induced MV disease with MR is often limited by thickened leaflets with restricted movement and subsequent risk of iatrogenic stenosis.

In patients with active or stable cancer and severe AS, both TAVI and SAVR can be considered based on life expectancy, age, prognosis, and disability following cancer treatment, with a trend towards more TAVI utilization.[185] TAVI procedural complication rates appear similar compared with those of control subjects without cancer.[186] To avoid futility, treatment decisions discussed by the Heart Team should involve the treating oncologists.[5,182]

6.4. Prophylaxis of rheumatic fever

Rheumatic heart disease remains the most common cause of death from VHD worldwide.[187] Prevention should preferentially target the first occurrence of acute rheumatic fever. Correct diagnosis and early antibiotic treatment of group A *Streptococcus* throat or skin infection is key for primary prevention. Large-scale screening combined with prophylaxis in children or adolescents with latent RHD appears to be an effective strategy to reduce the risk of disease progression and RHD prevalence.[188–190] In patients with established RHD, secondary long-term prophylaxis with benzathine benzyl penicillin 1.2 million international units (IU) every 3–4 weeks over 10 years is recommended to prevent recurrent episodes, especially in children and adolescents. Long-term prophylaxis into adulthood should be considered in high-risk patients according to the severity of VHD and exposure to group A *Streptococcus*.[191,192]

6.5. Cardiogenic shock and acute heart failure

Acute presentation or decompensation of VHD can result in cardiogenic shock due to rapid haemodynamic deterioration and altered cardiac function. Alternatively, pre-existing VHD can be a bystander of an acute cardiovascular condition further exacerbating circulatory impairment until the occurrence of cardiogenic shock. In this setting, assessment of the severity of VHD, as well as its contribution to acute HF, may be difficult. Evidence concerning acute VHD management in this context is scarce and only exists for the MV and AV.[193,194]

Hospital admission for acute decompensated AS is a frequent problem seen in up to 25% of AS hospitalizations.[195,196] However, only a minority of these patients (1.6%–3.2%) present with cardiogenic shock.[197,198] While intensive care treatment remains the cornerstone of haemodynamic stabilization and support, an intervention should be considered early, because it represents the only way to reverse progressive organ dysfunction due to low cardiac output. Balloon aortic valvuloplasty has been used in this context in the past, but has been largely replaced by TAVI in recent years, due to the high risk of severe AR and mortality in the acute setting.[199–201] Several large observational studies have established the feasibility of TAVI in patients with cardiogenic shock with similar device success, even if LVEF is low, although 30-day mortality remains higher (13%–19%) compared with routine TAVI.[194,197,198] Surgery represents the preferred treatment in patients with acute AR, while TAVI has only been described in individual cases or patients with a failed surgical valve (valve-in-valve). Fast pacing over a temporary pacemaker lead shortens the diastole and may temporarily improve haemodynamics until the intervention.[5,8]

Except for papillary muscle rupture, acute PMR rarely leads to cardiogenic shock and may be best treated by surgical valve repair or replacement. In contrast, increasing evidence supports the use of M-TEER in patients with acute ventricular SMR, particularly following acute myocardial infarction, due to lower mortality compared with surgery or medical treatment in propensity-matched analyses.[194,202,203] This strategy might also be helpful to facilitate weaning from mechanical circulatory support.

6.6. Palliative care

In some patients with advanced VHD not qualifying for surgical or transcatheter therapies, medical HF treatment remains the only, and sometimes best, available option. These patients usually present late, have extensive cardiac damage, develop terminal HF during the natural evolution of VHD, and are ineligible for mechanical circulatory support or heart transplantation (HTx). Early implementation of expert multidisciplinary palliative and end-of-life care, with the support of HF specialists,[204–206] reduces the number of hospitalizations and improves quality of life and symptom burden, in particular dyspnoea, pain, and anxiety.[207] Continuous co-ordination between all involved subspecialties, and transparent communication with the patient and their relatives, are key to ensure high quality of care.

7. Aortic regurgitation

7.1. Prevalence and aetiology

Chronic AR is mainly due to intrinsic abnormalities of the AV cusps and/or secondary to progressive dilatation of the aortic root and/or ascending aorta. In high-income countries, degenerative changes are the leading cause of AR, while RHD is more frequent in middle- and low-income countries.[12] Acute presentations are usually related to infective endocarditis or extension of aortic dissection into the aortic root. Chronic pure severe AR is more frequent in men and is associated with BAV and concomitant dilatation of the aorta in more than one-half of cases.[208]

7.2. Evaluation

During stepwise AR evaluation, the following aspects should be addressed: the severity of AR, its mechanism, and aetiology; the haemodynamic impact on LV function and pulmonary pressure; and evaluation of the ascending aorta. While echocardiography is the first-line modality, CMR and CCT are more accurate for the measurement of specific parameters (*Figure 4*). The results of the evaluation need to take into consideration the haemodynamic condition of the patient, particularly the blood pressure (BP), since high pressures can lead to overestimation of the regurgitant volume (RVol).

Assessment of AR severity with TTE follows an integrative approach considering qualitative, semi-quantitative, and quantitative parameters, but remains challenging.[45] Consequences of AR on LV size and function must be carefully assessed. Cut-offs for intervention are mostly based on two-dimensional (2D) echocardiographic measurements. However, 3D echocardiography and CMR allow more accurate

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evaluation of LV volumes and LVEF than 2D echocardiography, and are useful in borderline cases (*Figure 4*).[45,209] Strain imaging can be helpful in identifying subclinical LV dysfunction[209–211] and can therefore influence the optimal timing of intervention. Reduced longitudinal strain and contractile reserve at stress echocardiography,[212] elevated biomarkers (BNP),[213,214] and the presence of myocardial fibrosis detected by CMR need to be integrated in the decision-making process, even if not entirely validated yet.[209]

Given its close relationship with AV function, accurate measurements of the aortic diameter are required at all levels: the annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta.[8,215,216] The largest diameter is used to indicate the specific aortic phenotype: root phenotype, ascending phenotypes, and extended or mixed forms (see Supplementary data online, *Figure S1*).[8] The mechanism of AR and aortic diameters determine suitability for AV sparing or repair.[217,218]

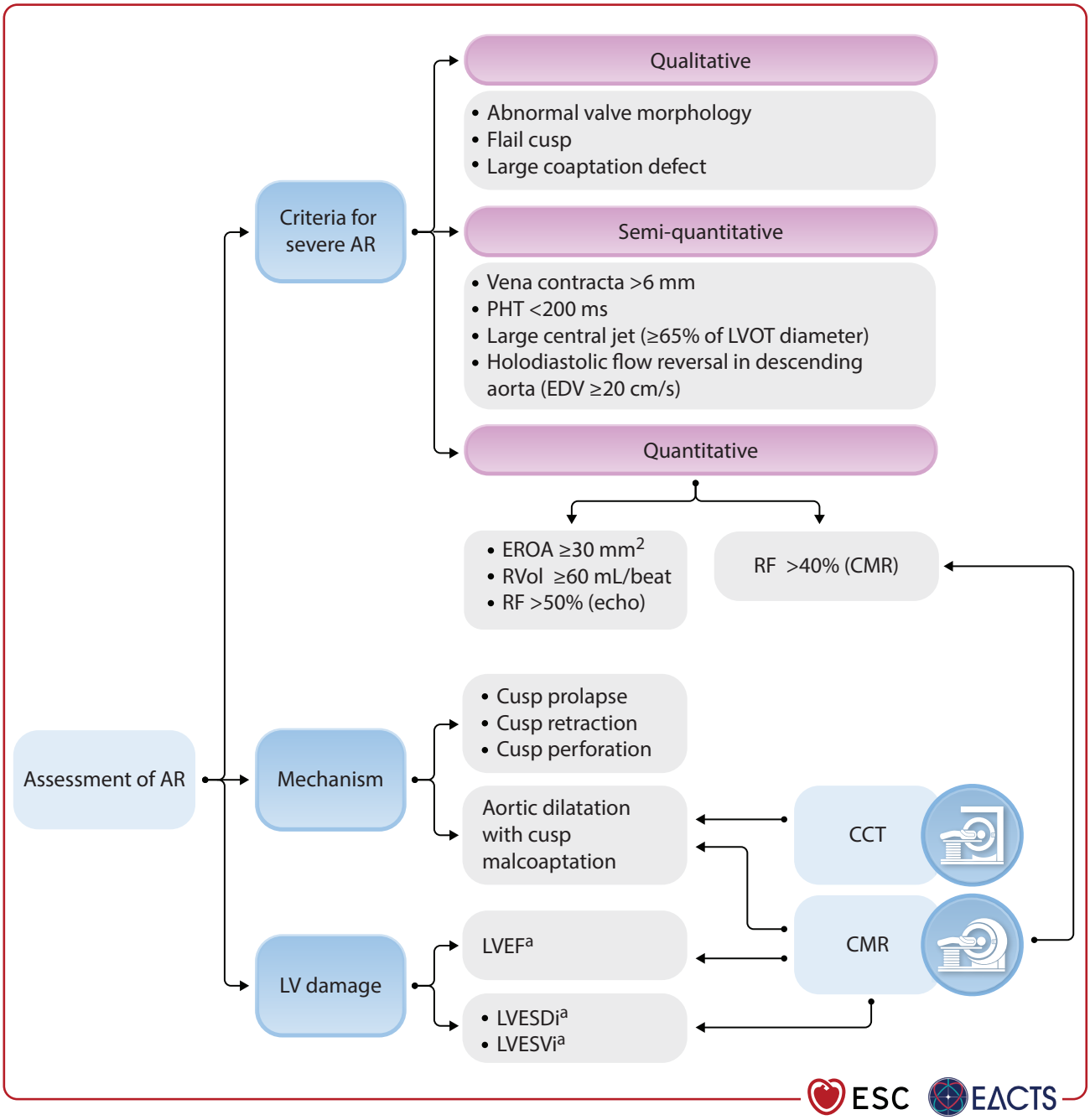

Figure 4 Imaging assessment of patients with aortic regurgitation. AR, aortic regurgitation; CCT, cardiac computed tomography; CMR, cardiac magnetic resonance; EDV, end-diastolic velocity; EROA, effective regurgitant orifice area; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESDi, left ventricular end-systolic diameter indexed to body surface area; LVESVi, left ventricular end-systolic volume indexed to body surface area; LVOT, left ventricular outflow tract; PHT, pressure half-time; RF, regurgitant fraction; RVol; regurgitant volume. [a]See *Recommendation Table 3* for specific cut-offs.

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The morphology of the AV represents a critical aspect in the diagnosis and treatment of AR. Pure AR in the context of BAV uncommonly manifests with normal aortic diameters, being more often associated with a dilated ascending aorta and/or root. It is important to define the valve phenotype to determine the repair probability and long-term result of AV repair or AV-sparing procedures. The degree of symmetry is an important predictor of BAV reparability with better long-term results in more symmetric phenotypes.[219–221]

7.3. Medical therapy

Medical therapy, especially angiotensin-converting enzyme-inhibitors (ACE-Is) or dihydropyridine calcium channel blockers, may provide symptomatic improvement in individuals with chronic severe AR for whom surgery is not feasible or contraindicated. The value of ACE-Is or dihydropyridines in delaying surgery in the presence of moderate or severe AR in asymptomatic patients has not been established, and their use is not recommended for this indication. The use of beta-blockers increases the length of the diastole and therefore the RVol, and should be used with caution if indicated for another reason. However, beta-blockers can be used along with ACE-Is or angiotensin receptor blockers (ARBs) after surgery, if indicated (systolic HF or heart rate control).[222,223]

7.4. Indications for intervention

Acute severe AR usually requires immediate surgery depending on the aetiology, such as infective endocarditis or spontaneous, traumatic, or iatrogenic aortic dissection.[5,8] Surgery for the treatment of chronic severe AR is indicated depending on symptoms and/or the effects of the RVol on LV size and function (see *Recommendation Table 3* and *Figure 5*). The presence of associated aortic dilatation dictates surgery, irrespective of AR severity. When the patient is symptomatic and AR severe, surgery is recommended unless the anticipated surgical risk is prohibitive.[224–228] Concomitant surgical treatment of severe AR is also recommended, irrespective of symptoms, in patients requiring CABG, ascending aorta surgery, or any other cardiac surgical procedures.[229,230]

For the asymptomatic patient with severe AR, indications for surgery are based on the degree of functional impairment of the LV [LVEF ≤50%, left ventricular end-systolic diameter (LVESD) >50 mm, or left ventricular end-systolic diameter indexed to body surface area (BSA) (LVESDi) >25 mm/m^2, especially in those with small BSA (BSA <1.68 m^2) and elderly patients with low ventricular compliance].[226,228,231–234] If surgery is deemed low risk, there is observational evidence from echocardiographic studies that early intervention might be beneficial for long-term prognosis when LVEF is ≤55%, LVESDi is >22 mm/m^2, and/or left ventricular end-systolic volume indexed to BSA (LVESVi) is >45 mL/m^2.[235–239] A volumetric cut-off value of LVESVi ≥43 mL/m^2 using CMR was recently proposed to guide the management of asymptomatic patients[240,241] and appears to have better predictive value than LV diameter.[242] Surgery may also be discussed in selected low-risk asymptomatic patients with significant LV dilatation (left ventricular end-diastolic diameter >65 mm) and progressive increase of LV diameters and/or decrease of LVEF during follow-up. Exercise testing should be performed, when feasible, in patients with severe AR who do not report symptoms and do not meet criteria for surgery.[212]

AV replacement is still the standard surgical approach in most AR cases (see *Section 14.1* regarding prosthesis type considerations). However, owing to a better understanding of the pathophysiology of the aortic root (see Supplementary data online, *Figure S1*) paralleled with favourable long-term results, valve-sparing aortic root replacement (VSARR) and AV repair are increasingly performed in centres with appropriate expertise (*Figure 5*).[243–255] In patients with root enlargement and good tissue quality (i.e. pliable AV cusps with normal motion), a valve-sparing procedure has been demonstrated to be superior to the use of a composite valve graft (Bentall procedure) in terms of long-term mortality and overall morbidity (thromboembolism and endocarditis, with similar need for reoperation),[250–253,255–257] and should be therefore favoured by experienced centres, in particular in patients with an estimated long life expectancy.[258] Valve preservation or valve repair should also be considered for patients with BAV based on age, anatomical presentation, and centre experience (*Figure 5*).[220,245,246,259]

When performed by experienced surgeons in well-selected young individuals, pulmonary autograft implantation (Ross operation) may also be a good alternative to prosthetic valve replacement.[260–263]

TAVI may be considered at experienced centres for selected patients with AR who are ineligible for surgery. The use of non-dedicated transcatheter valves for this indication is off-label and associated with an increased risk of valve malpositioning and residual AR, with consecutively higher rates of second valve implantation (about 10%) or surgical conversion, as compared with TAVI in AS.[264–268] Dedicated devices appear to minimize the risk of valve migration and residual AR in selected patients, but are associated with a high new permanent pacemaker implantation rate (24%).[267–269]

Aortic dilatation is closely linked to AR. Dedicated ESC Guidelines give guidance regarding the evaluation and management of aortic root and ascending aortic dilatation.[8] The aortic phenotype (see Supplementary data online, *Figure S1*), degree and rate of progression of aortic dilatation, and the underlying aetiology all affect timing of surgery, with the main indication being maximum aortic diameter.[270–272] Dilation of the aortic root, which typically occurs in Marfan syndrome and other patients with connective tissue disease, has a worse prognosis compared with isolated dilatation of the ascending aorta and requires closer surveillance.[270–272] Surgery is recommended in all patients with a maximal aortic root or ascending aneurysm diameter of ≥55 mm. In the presence of additional risk factors, a threshold of 50 mm may be considered for selected low-risk patients treated at experienced centres.[8] If the patient has an established indication for AV surgery (due to AR or AS), concomitant surgery of the aortic root or the ascending aorta should be considered at a diameter of ≥45 mm. This threshold has been more clearly demonstrated in patients with BAV and should also be based on the patient's height[273] or specific intraoperative findings, such as the shape and thickness of the aortic wall.

7.5. Follow-up

A multimodality imaging approach[45,274] and biomarkers like BNP[213,214] might help identify patients at increased risk of LV damage early and guide the appropriate timing of intervention. Yearly follow-up is recommended in asymptomatic patients with severe AR. Closer follow-up (3–6 months) is recommended for those approaching thresholds for surgery, or showing a progressive dilatation of the LV or decrease of LVEF. Cardiac magnetic resonance can be especially useful in such a setting. Patients with moderate AR should be followed on a yearly basis, with echocardiography performed every 2 years.

When a dilated ascending aorta is initially diagnosed by TTE, a multislice electrocardiographic-triggered CCT/CMR scan is recommended

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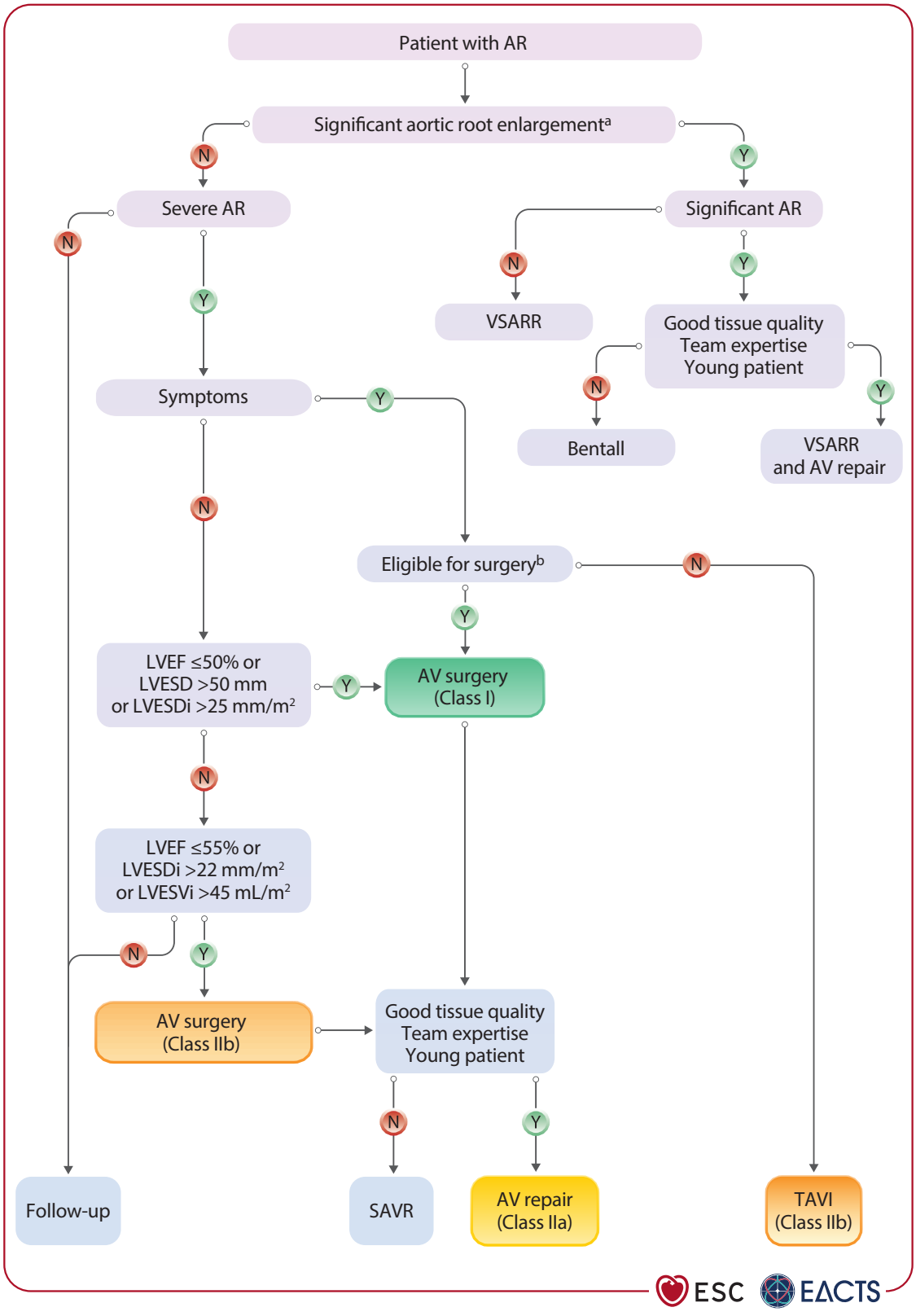

Figure 5 Management of patients with aortic regurgitation. AR, aortic regurgitation; AV, aortic valve; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to body surface area; LVESVi, left ventricular end-systolic volume indexed to body surface area; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve replacement; VSARR, valve-sparing aortic root replacement. [a]Indications for surgery on the root/ascending aorta are described in the *2024 ESC Guidelines for the management of peripheral arterial* and *aortic diseases*.[8] [b]Concomitant replacement of the aortic root or ascending aorta should be considered if the maximal diameter is ≥45 mm and the predicted surgical risk is low.

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to confirm maximal diameter, rule out isolated single sinus dilatation, and provide a baseline reference. When the baseline aortic diameter is >45 mm, a second TTE examination is recommended at 6 months to confirm the stability of the finding, followed by serial examinations on a yearly basis thereafter.[275] Any increase of >3 mm should be validated by CT angiography/CMR and compared with baseline data.[275] After repair of the ascending aorta, patients with Marfan syndrome and other connective tissue diseases remain at risk for dissection of untreated portions of the aorta, and require lifelong regular multidisciplinary follow-up at an expert centre.[8]

7.6. Special patient populations

Patients with concomitant VHD and those with AS combined with AR are discussed in *Section 13.3.3*. In patients with moderate AR and indication for CABG or MV surgery, the decision to treat the AV should be discussed by the Heart Team based on the aetiology of AR and other clinical factors, like the estimated life expectancy and the operative risk, as data show that progression of moderate AR may be very slow.[276]

The presence of aortic dilation and AR in asymptomatic patients poses the problem of limiting the level of physical activity, but consistent data are lacking. Current recommendations for participation in competitive sport are restrictive, especially regarding isometric exercise in patients with connective tissue disease,[277] while a more liberal approach is likely to be appropriate in other patients.

Given the familial risk of thoracic aortic aneurysms, screening with appropriate imaging studies and testing for genetic abnormalities in first-degree relatives is indicated in patients with connective tissue disease.[278] Since aortic dilation is present in ~10% of first-degree relatives of patients with a BAV, it is also considered appropriate to encourage echocardiographic screening in this specific population.[275,279]

Recommendation Table 3 — Recommendations on indications for intervention in severe aortic regurgitation (see also Supplementary data online, *Evidence Tables 4–8*)

Recommendations	Class[a]	Level[b]
Severe aortic regurgitation		
AV surgery is recommended in symptomatic patients with severe AR regardless of LV function.[224–228]	I	B
AV surgery is recommended in asymptomatic patients with severe AR and LVESD >50 mm or LVESDi >25 mm/m^2 [especially in patients with small body size (BSA <1.68 m^2)] or resting LVEF ≤50%.[226,228,231,233,234]	I	B
AV surgery is recommended in symptomatic and asymptomatic patients with severe AR undergoing CABG or surgery of the ascending aorta.	I	C
AV repair should be considered in selected patients with severe AR at experienced centres, when durable results are expected.[220,245,246,259]	IIa	B
AV surgery may be considered in asymptomatic patients with severe AR and LVESDi >22 mm/m^2,[226,228,231–234] or LVESVi[c] >45 mL/m^2 [especially in patients with small body size (BSA <1.68 m^2)],[235–241] or resting LVEF ≤55%, if the surgical risk is low.	IIb	B
TAVI may be considered for the treatment of severe AR in symptomatic patients ineligible for surgery according to the Heart Team, if the anatomy is suitable.[264,265,268,269]	IIb	B
Concomitant surgery of the ascending aorta		
Valve-sparing aortic root replacement is recommended in young patients with aortic root dilatation at experienced centres, when durable results are expected.[247,250–253,255]	I	B
When AV surgery is indicated and the predicted surgical risk is low, replacement of the aortic root or ascending aorta should be considered if the maximal diameter is ≥45 mm.[d]	IIa	C

AR, aortic regurgitation; AV, aortic valve; BSA, body surface area; CABG, coronary artery bypass grafting; CMR, cardiac magnetic resonance; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to BSA; LVESVi, left ventricular end-systolic volume indexed to BSA; TAVI, transcatheter aortic valve implantation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Using echocardiography or CMR.
[d]Considering age, BSA, the aetiology of the valvular disease, the presence of a bicuspid AV, and the intraoperative shape and thickness of the ascending aorta.

8. Aortic stenosis

8.1. Prevalence and aetiology

Even if AS is the most common primary valve lesion referred for intervention in Europe and North America,[12] underdiagnosis and undertreatment remain relevant concerns.[10] Degenerative pathogenesis with cusps calcification is most common in developed countries and prevalence is rising rapidly because of the ageing population.[11,12,187] BAVs, or more rarely unicuspid AVs, are prone to earlier degeneration, constitute the dominant valve morphology in younger patients requiring AV replacement, and are frequently associated with dilatation of the aortic root or ascending aorta.[280,281] In low- and middle-income countries, rheumatic aetiology remains frequent and AS usually presents combined with rheumatic MV disease.[282]

8.2. Evaluation

8.2.1. Echocardiography and cardiac computed tomography

Aortic stenosis is a disease slowly evolving from mild to severe valve obstruction as a consequence of increasing valve fibrosis and calcification, although progression accelerates as haemodynamic severity increases.[283]

Echocardiography is key to confirm the diagnosis and allows comprehensive assessment of the anatomy and severity of stenosis. Evaluation of the haemodynamic consequences on cardiac function and geometry, and the detection of aortic pathology or concomitant valve disease, provide important prognostic information that may influence management.[284] Staging of extravalvular damage has been proposed,[53] but it may be difficult to attribute other cardiac abnormalities to AS itself, because comorbidities are frequent in patients with AS and the observed damage may not occur in the expected chronological sequence. However, the detection of concomitant cardiac conditions [e.g. HF with preserved EF (HFpEF), amyloidosis, or hypertrophic

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cardiomyopathy] may help to optimize medical treatment before and after valve intervention.[285,286]

Current European recommendations for the echocardiographic grading of AS rely on measurement of the mean pressure gradient (most robust parameter), peak transvalvular velocity (V_{max}), and effective AVA. Although AVA is theoretically the ideal parameter for assessing severity, there are numerous technical limitations associated with its calculation.[284,287]

Aortic stenosis may be further categorized according to flow state based on stroke volume index (SVi) when there is discordance between echocardiographic parameters (*Figure 6*). A threshold of 35 mL/m^2 is conventionally accepted to discern low from normal flow, although sex-specific thresholds have been proposed.[292]

Concordant criteria:

- High-gradient AS [mean gradient ≥40 mmHg, V_{max} ≥4.0 m/s, AVA ≤1 cm^2 (or ≤0.6 cm^2/m^2)] is considered severe irrespective of LV function and flow conditions.

Discordant criteria:

- Low-flow, low-gradient AS with reduced LVEF (mean gradient <40 mmHg, AVA ≤1 cm^2, SVi ≤35 mL/m^2, LVEF <50%).
- Low-flow, low-gradient AS with preserved LVEF (mean gradient <40 mmHg, AVA ≤1 cm^2, SVi ≤35 mL/m^2, LVEF ≥50%).
- Normal-flow, low-gradient AS with preserved EF (mean gradient <40 mmHg, AVA ≤1 cm^2, SVi >35 mL/m^2, LVEF ≥50%).
- Discordant high-gradient AS (mean gradient ≥40 mmHg, AVA >1 cm^2).

Patients with discordant normal-flow, low-gradient AS usually have moderate stenosis.[293–295] Discordant high-gradient AS is considered severe if not caused by a reversible high-flow status.[296–298]

In patients with low-flow, low-gradient AS with reduced LVEF, dobutamine stress echocardiography (DSE) can help to discriminate between pseudo-severe and true severe AS in the presence of flow reserve (increase in stroke volume of ≥20%).[289,299]

Cardiac computed tomography calcium AV scoring is readily available and provides important adjunctive information in patients with low-flow, low-gradient AS because it correlates with haemodynamic severity, progression, and clinical outcomes.[300,301] Values of >2000 Agatston units (AU) in men and >1200 AU in women indicate severe AS with high sensitivity and specificity (~85%).[302,303] While higher thresholds (men >3000 AU, women >1600 AU) are very specific, severe AS becomes unlikely in patients with calcium AV scoring of <1600 AU in men and <800 AU in women.[284,302,303] Cautious interpretation is required in patients who can develop severe AS without pronounced AV calcification such as in BAV, concomitant amyloidosis, and predominantly fibrotic stenosis associated with post-rheumatic, radiation-induced and inflammatory disease.[304–308]

In low-flow, low gradient AS with reduced LVEF, CCT AV calcium scoring and DSE provide complementary information. If findings are equivocal, an integrated assessment considering all available clinical, morphological, and haemodynamic factors is required.

8.2.2. Additional diagnostic and prognostic parameters

The ratio of the LVOT to the AV Doppler jet velocity time integral (VTI, dimensionless index or velocity ratio) does not require calculation of LVOT area and may assist evaluation when other parameters are equivocal (<0.25 suggests that severe AS is highly likely).[309]

Assessment of GLS can be useful for risk stratification[310] and evaluation of extravalvular cardiac damage.[311,312] It provides additional information regarding LV function and a threshold of −15% may contribute to identifying patients with severe asymptomatic AS at increased risk of clinical deterioration or premature mortality.[59]

Estimated valvuloarterial impedance has been shown to be prognostic of adverse clinical outcomes before and after valve replacement.[313–315]

Transoesophageal echocardiography (TOE) allows morphological evaluation of the valve, planimetry of AVA and assessment of potential subvalvular obstruction (unless there is acoustic shadowing caused by calcification), and evaluation of concomitant valve disease, and can be of value for peri-procedural imaging in challenging clinical or anatomical scenarios.[316]

Natriuretic peptides can be used to arbitrate the sources of symptoms in patients with multiple potential causes and help to identify those with high-risk asymptomatic AS who may benefit from early intervention.[97,317]

Exercise testing can unmask symptoms and haemodynamic intolerance (fall in BP >20 mm Hg) and is recommended for risk stratification in asymptomatic patients with severe AS.[102,318] Exercise echocardiography may provide additional prognostic information by assessing the increase in mean pressure gradient and change in LV function.[319] Cardiopulmonary exercise testing, eventually complemented by echocardiography, can help to uncover cardiac dysfunction in asymptomatic patients, discriminate cardiac from pulmonary limitation or deconditioning in patients with non-specific symptoms, and inform risk stratification.[105,106,320,321]

Cardiac magnetic resonance is used to identify altered global LV geometry due to remodelling, as well as to quantify myocardial scarring and diffuse fibrosis, which are associated with the occurrence of adverse events.[322–324]

Transthyretin cardiac amyloidosis may coexist with AS in elderly patients and the two conditions may causally interrelate.[325] When transthyretin cardiac amyloidosis is suspected, the presence of monoclonal protein in serum and urine should be excluded using immunofixation and quantitative determination of free light chains, and diagnosis ascertained by means of diphosphonate scintigraphy.[326] Despite the limited long-term prognosis associated with cardiac transthyretin amyloidosis, patients with concomitant severe AS usually benefit from valve intervention.[327]

LV catheterization is not recommended unless there are symptoms and signs of severe AS, and non-invasive investigations are inconclusive.

8.2.3. Procedural planning

Cardiac computed tomography is key to determining suitability for TAVI and planning the procedure. It is the preferred imaging tool to assess AV anatomy including annulus size, dimensions of the aortic root and ascending aorta, the extent and distribution of valve and LVOT calcification, the distance of coronary ostia from the annular plane, optimal fluoroscopic projections for transcatheter valve deployment, and the feasibility of vascular access.[49,328,329]

Transoesophageal echocardiography (TOE), which is more operator-dependent and does not allow assessment of coronary and peripheral vascular anatomy, or CMR may be considered when CCT is difficult to interpret or relatively contraindicated (e.g. in patients with renal failure).[330,331]

8.3. Medical therapy

No medical therapies have been shown to influence the natural history of AS to date. Neither statins, which demonstrated favourable effects in pre-clinical studies,[332–334] nor substances

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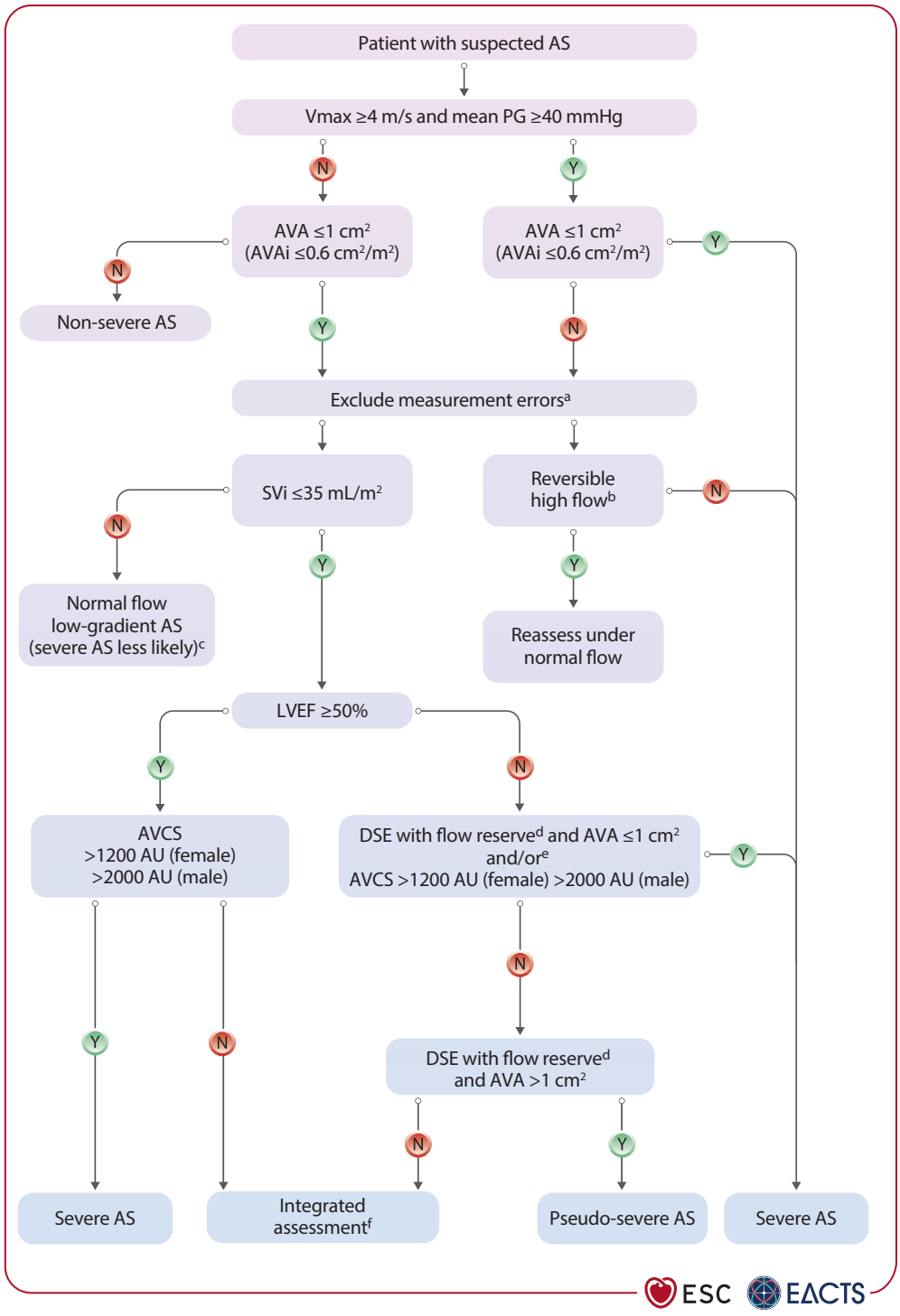

Figure 6 Integrative imaging assessment of patients with aortic stenosis. AS, aortic stenosis; AU, Agatston units; AV, aortic valve; AVA, aortic valve area; AVAi; aortic valve area indexed for body surface area; AVCS, aortic valve calcium score; CCT, cardiac computed tomography; CT, computed tomography; DSE, dobutamine stress echocardiography; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MRI, magnetic resonance imaging; mean PG, mean pressure gradient; SVi, stroke volume indexed for BSA; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; V_{max}, peak transvalvular velocity. [a]In particular, verify LVOT diameter and multiwindow Doppler interrogation. [b]High flow may be reversible (anaemia, hyperthyroidism, or arteriovenous fistulae). Upper limit of normal flow using pulsed Doppler: cardiac index 4.3 L/min/m^2, SVi 58 mL/m^2.[288] [c]Available evidence refers to patients with preserved LVEF. Check for bradycardia or uncontrolled hypertension, which may lead to prolonged ejection time and reduced flow rate. Depending on symptoms, integrated assessment complemented by CCT AV calcium scoring may be pursued. [d]Flow reserve: ≥20% increase in stroke volume in response to low-dose dobutamine or if change in stroke volume of 10%–20%, calculate projected AVA.[289,290] [e]If one test is not conclusive, complement diagnostics with the other test. [f]Based on clinical judgement (typical symptoms without other explanation), morphological valve changes, LV hypertrophy (in absence of coexistent hypertension), and consistent findings using different modes of assessment [TTE and TOE, invasive assessment, AV planimetry by CT or MRI (cut-off 1.2 cm^2)][291].

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targeting calcification pathways alter disease progression.[335,336] Coexistent hypertension should be treated to avoid additional afterload, preferably using renin-angiotensin system blockers, although careful titration is required to avoid symptomatic hypotension.[337]

In patients with symptomatic severe AS and HF, initiation of medical therapy or temporary improvement in symptoms should not delay intervention. Medication frequently requires re-adjustment following valve intervention and preventive therapies should be implemented according to current Guidelines.[338] In patients with persisting HF and/or reduced LVEF, medical therapy should be introduced before and up-titrated after valve intervention according to the current HF Guidelines.[339,340]

8.4. Indication for intervention

8.4.1. Symptomatic severe aortic stenosis

Symptomatic severe AS has an unfavourable prognosis if left untreated, and early intervention is strongly recommended in all patients with an estimated life expectancy exceeding 1 year[10] (*Figure 7*).

Intervention is recommended in all eligible symptomatic patients with high-gradient severe AS. However, management of patients with low-gradient AS is more challenging:

- Low-flow, low-gradient AS with reduced LVEF: reduced LV function usually improves after intervention if it is predominantly caused by excessive afterload.[341–343] However, improvement is unlikely if the primary cause is fibrosis due to myocardial infarction or cardiomyopathy. Intervention is recommended when severe AS is confirmed by CCT (calcium scoring) or stress echocardiography,[341] while patients with pseudo-severe AS should receive GDMT.[339,344] Although the absence of flow reserve is associated with increased surgical and long-term mortality, both modes of intervention improved LVEF and clinical outcomes in observational studies.[341,342,345–347]
- Low-flow, low-gradient AS with preserved LVEF: outcomes are improved with intervention (either TAVI or SAVR) compared with medical treatment alone in patients with low-flow, low-gradient AS and preserved LVEF.[348,349] Intervention should therefore be considered in patients with symptoms after careful confirmation that AS is severe.
- Normal-flow, low-gradient AS with preserved LVEF: prognosis of these patients is similar to that of moderate AS. Unless multimodality diagnostic evaluation clearly suggests severe AS, regular clinical and echocardiographic surveillance is recommended.[293,294,350]

8.4.2. Asymptomatic severe aortic stenosis

Up to 40% of patients with severe AS do not report symptoms at the time of diagnosis.[351,352] In roughly one-third of these, exercise testing can uncover symptoms or reduced exercise capacity attributable to AS,[102,103,318] and such patients should be treated as symptomatic. However, exercise testing is not always feasible because of frailty or impaired mobility.[353] Intervention is recommended in asymptomatic patients with severe AS and an LVEF of <50% without another cause.[14,102,318,319,354–360] For patients with severe high-gradient AS and no adverse prognostic features, close active clinical surveillance, so-called 'watchful waiting', has previously been the default management strategy. However, four RCTs comparing early AV intervention with clinical surveillance suggest that early intervention should be considered as an alternative in patients at low procedural risk.[360–363] This approach is reinforced if additional adverse prognostic features (very high V_{max},[14,353,364] elevated natriuretic peptides,[97,317,365,366] severe valve calcification,[303,364] rapid V_{max} progression,[353,364] or LVEF of <55%[14,354,356–359]) are present. Restricted local resources (that may impede close surveillance) or long waiting lists (that preclude prompt treatment when symptoms develop) are further arguments favouring an early intervention.

The Evaluation of TAVR Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis (EARLY TAVR) trial[360] randomized 901 patients to early TAVI or clinical surveillance and demonstrated a reduction of 50% in the primary composite endpoint of all-cause mortality, stroke, or unplanned hospitalization for cardiovascular causes associated with pre-emptive intervention.[360] The result was driven by 26.2% of the patients in the clinical surveillance group who converted to TAVI within 6 months of randomization due to the development of symptoms or adverse prognostic factors. There was no significant difference in strokes and all-cause mortality over 5-year follow-up.

In the Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS (EVoLVeD) RCT, which included 224 asymptomatic patients with severe AS and myocardial fibrosis (late gadolinium enhancement on CMR), early valve intervention (with SAVR or TAVI) failed to reduce the incidence of all-cause death or unplanned AS-related hospitalization compared with clinical surveillance.[361] However, the study was underpowered and the median time to intervention was prolonged to 5 months in the experimental arm.

Two previous smaller trials compared early SAVR with clinical surveillance. In the Randomized Comparison of Early Surgery vs Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY) trial (145 patients), there was a reduction in all-cause mortality following early SAVR over a mean follow-up of 6.2 years.[362] In the Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR) trial (157 patients), a reduction in the composite primary endpoint was noted after a mean follow-up of 2.5 years with a significant reduction in HF hospitalizations and mortality at long-term follow-up.[363,367] Limitations of these surgical studies included their small sample sizes, enrolment of selected young populations at low surgical risk (mean ages 64 and 67 years, respectively), and inclusion of patients with mostly very severe AS.

A meta-analysis of the four RCTs showed that early intervention is associated with a significant reduction in unplanned cardiovascular or HF hospitalization and stroke, but not all-cause or cardiovascular mortality. Limitations of this analysis include the heterogeneity of the pooled trials and lack of granularity with respect to specific events owing to the study-level analysis.[368]

Additional RCTs (NCT04204915 and NCT03972644) will further inform and refine the management of patients with severe asymptomatic AS.

8.4.3. Moderate aortic stenosis

Surgical intervention for moderate AS should only be performed in patients undergoing CABG,[369] surgery of the ascending aorta or other valve disease (see *Section 13*). There is evidence of an association between moderate AS and adverse outcomes in patients with and without HF with reduced EF (HFrEF),[370–372] but it is unknown whether this is causal or related to comorbidities. In an early terminated trial randomizing 178 patients with moderate AS and HFrEF to TAVI or clinical surveillance, no differences with respect to hard clinical endpoints were

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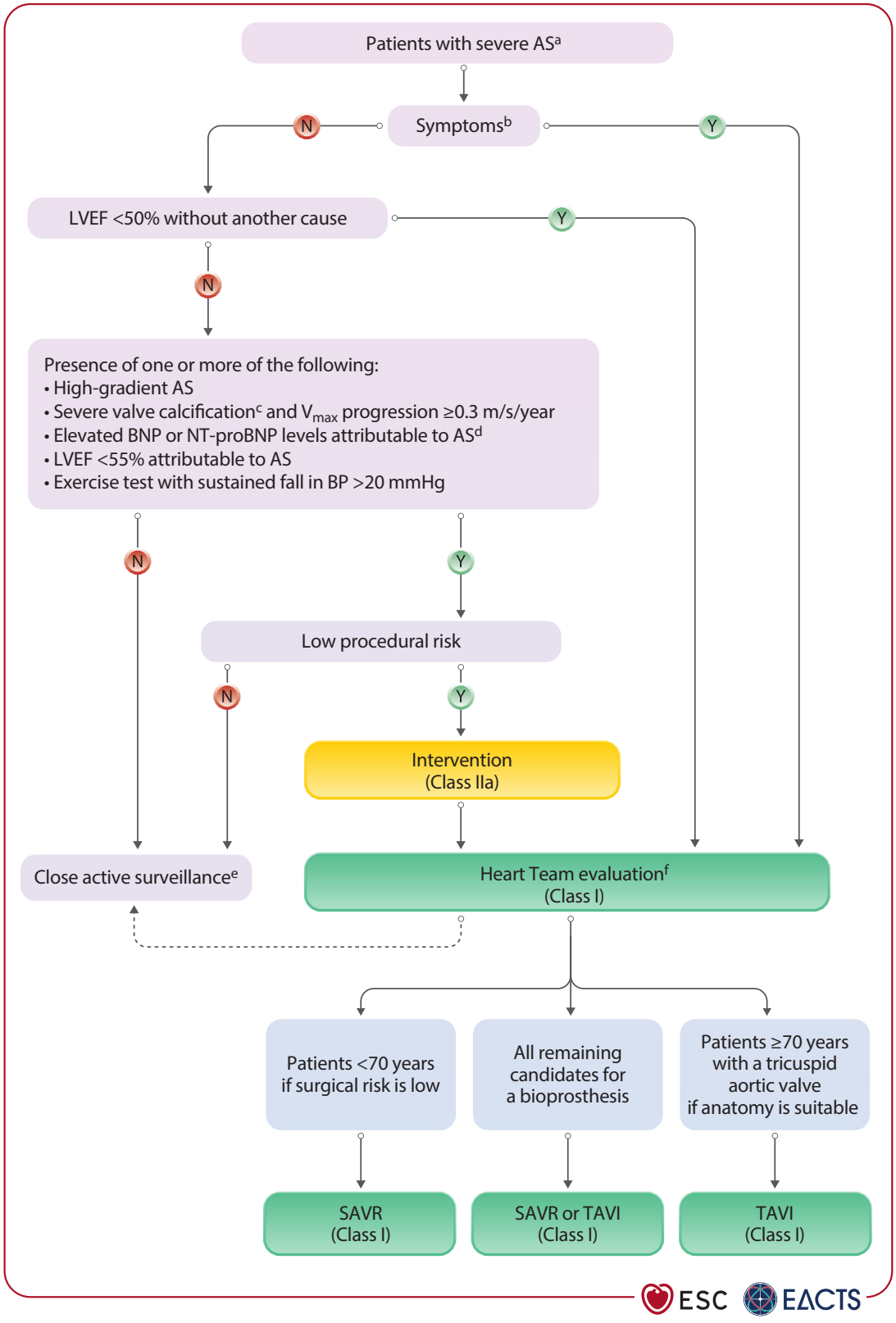

Figure 7 Management of patients with severe aortic stenosis. AS, aortic stenosis; AVCS, aortic valve calcium score; BNP, brain natriuretic peptide; BP, blood pressure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; V_{max}, peak transvalvular velocity. [a]Integrative imaging assessment of AS (*Figure 6*). [b]Confirmed by a normal exercise test, if feasible. [c]AVCS >2000 in men, >1200 in women. [d]More than three times age- and sex-corrected normal range. [e]Educate patient and reassess at least every 6 months (or promptly if symptoms occur). [f]Heart Team assessment based upon individual patient factors (*Figure 9*; *Recommendation Table 4*). Dashed arrow only applies to asymptomatic patients.

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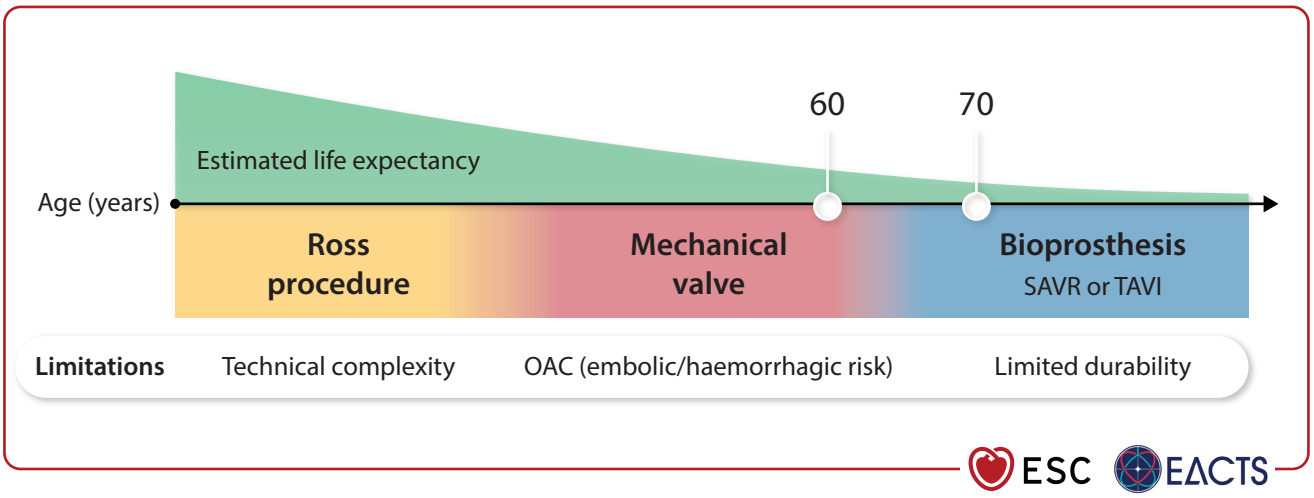

Figure 8 Aortic valve treatment options. OAC, oral anticoagulation; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

found, while patients undergoing TAVI had improved quality of life (change in KCCQ of 12.8 ± 21.9 points vs 3.2 ± 22.8 points; $P = 0.018$).[373] Ongoing trials are expected to provide new insights (NCT04889872 and NCT05149755).

8.5. Treatment options

The mode of AV intervention depends on the estimated life expectancy, expected prosthesis durability, patient preference, and specific trade-offs associated with different treatment options (*Figure 8*). Most patients with AS undergoing valve intervention in Europe and North America receive a BHV (by either SAVR or TAVI).[374] BHVs do not require long-term anticoagulation but have limited durability that varies between devices and is inversely associated with age.[375] MHVs are durable but require long-term anticoagulation, with associated thromboembolic and bleeding risks.[260,376] In general, an MHV should be preferred in patients aged <60 years and a BHV in patients aged >65 years in aortic position (see *Section 14.1*).

The Ross procedure (replacement of the AV with the patient's pulmonary autograft combined with homograft pulmonary valve replacement) is associated with excellent long-term survival when performed in selected patients at centres with high expertise.[260,263,377,378] Although a valuable surgical option in young patients with prolonged life expectancy in whom anticoagulation is undesirable or contraindicated, it is associated with procedural complexity and the need for reintervention in ~15% of patients within 15 years (*Figure 8*).[263,377]

Balloon aortic valvuloplasty may be rarely considered as a bridge to TAVI or SAVR in carefully selected patients with decompensated AS, and in those with severe AS who require urgent high-risk non-cardiac surgery (NCS) (see *Section 15.2.1*). The procedure carries significant risks of acute complications.[379]

A substantial increase in the number of patients undergoing AV intervention has been observed over the past decade as a consequence of the introduction of TAVI, improved diagnostic techniques, and evolving indications for intervention.[374,380–383] Nevertheless, there is still wide variation in worldwide access to TAVI as a result of high device costs in comparison with surgical prostheses and variation in healthcare resources and reimbursement systems between countries.[384–386] In addition, registries suggest that late referral and undertreatment remain frequent.[12,387]

8.5.1. The mode of intervention in candidates for a bioprosthesis

The two modes of BHV replacement, TAVI and SAVR, have been compared in RCTs across the spectrum of surgical risk in predominantly elderly patients with tricuspid AS.

In patients unsuitable for surgery, TAVI was superior to medical therapy with a number-needed-to-treat of five to prevent one death at 1-year follow-up.[388] Subsequently, RCTs showed non-inferiority of TAVI compared with SAVR in patients at high,[389–391] intermediate,[3,392,393] and low surgical risk,[1,394,395] with comparable longer-term outcomes demonstrated during follow-up periods ranging from 4 to 10 years.[2,4,396–398] Of note, the majority of patients included in RCTs were male, while patients with low-flow low-gradient AS or adverse anatomical characteristics (including BAVs or complex CAD) were excluded per protocol.

Meta-analyses of RCTs show a risk reduction in all-cause death and disabling stroke with TAVI in low-risk patients at 1 year, but no differences to SAVR at longer-term follow-up or in patients at intermediate or high surgical risk.[399,400] The early benefit of TAVI in low-risk patients has since been corroborated in the investigator-initiated Randomized, Multicenter, Event-Driven Trial of TAVI vs SAVR in Patients with Symptomatic Severe Aortic-Valve Stenosis (DEDICATE), which met its non-inferiority target with a composite of death and stroke rate at 1 year of 5.4% in the TAVI group vs 10.0% in the SAVR group [hazard ratio (HR), 0.53; 95% confidence interval (CI), 0.35–0.79] and all-cause death rates of 2.6% and 6.2% (HR 0.43; 95% CI, 0.24–0.73), respectively.[395]

Rates of vascular complications and paravalvular leak (PVL) are consistently higher after TAVI despite refined transcatheter heart valve (THV) designs, whereas severe bleeding, acute kidney injury, and new-onset AF are more frequent after SAVR.[2,4,399,401] Even though PVL has been associated with adverse clinical outcomes,[402,403] it does not seem to impact the comparison of clinical outcomes between TAVI and SAVR in RCTs.[2,4,395]

New pacemaker implantations are more frequent after TAVI, particularly when using self-expanding valves.[3,394,404] Conflicting data exist regarding the long-term impact of new pacemaker implantation or new-onset left bundle branch block following AV intervention.[405–407] Patients undergoing TAVI have quicker recoveries, shorter hospital

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stays, and more rapid improvements in quality of life compared with those who undergo SAVR.[1,2,408,409]

Available data do not suggest systematic differences in durability between the two treatment modalities. Randomized controlled trials and observational studies have reported comparable rates of BHV failure related to SVD with transcatheter and surgical valves up to 10 years.[2,398,410] However, potential selection and survival bias, the use of variable definitions of SVD, limited follow-up durations, differential attrition rates,[2,4,396,400] competing risk of death, and the use of multiple valve types in the surgical arms of RCTs may limit direct comparison.[411]

Although conclusive evidence is still lacking, concomitant non-complex CAD can be addressed either by CABG or PCI, while complex CAD favours CABG (see *Section 6.1*). In the only RCT comparing these two strategies, the transcatheter valve and vessels (TCW) trial, randomization of patients with severe AS and concomitant CAD to FFR-guided PCI plus TAVI resulted in fewer deaths and major bleeding events compared with combined SAVR plus CABG at 12 months.[412] However, inferences from trial results are limited due to early termination, modest sample sizes, event rates deviating from those observed in registries and other RCTs, and a low prevalence of complex CAD.

8.5.1.1. Age and life expectancy

The relationship between estimated life expectancy and prosthetic heart valve durability determines the likelihood of a future reintervention. Although life expectancy may be a theoretically better guide than age alone for treatment decisions, it is difficult to estimate for an individual patient owing to large geographical (https://ghdx.healthdata.org/record/ihme-data/gbd-2019-life-tables-1950-2019) and interindividual variability.[413] In combination with cardiac and extracardiac comorbidities, as well as anatomical factors, age contributes to risk estimation and represents a pragmatic surrogate for life expectancy. In addition, age thresholds characterize the populations enrolled in RCTs better than life expectancy. It is notable that younger patients with AS seem to have lower life expectancy than the general population despite valve replacement, whereas life expectancy almost normalizes after treatment in older cohorts.[414,415] While several trials compared TAVI with SAVR in study populations aged 70–85 years accross the surgical risk spectrum, the representation of patients aged <70 years in RCTs is low and therefore evidence limited.[1,394,395,416]

8.5.1.2. Anatomical features

The advantages of TAVI demonstrated in RCTs are largely confined to patients treated via the transfemoral approach.[401] While SAVR remains the preferred treatment option when iliofemoral artery disease precludes transfemoral TAVI, TAVI via a non-transfemoral access (transaxillary, transcarotid, transcaval, transinnominate, or transapical) constitutes an alternative supported by observational data in patients unsuitable for surgery.[417–423]

Other anatomical factors that favour SAVR or led to exclusion of patients from RCTs comparing TAVI with SAVR are (*Figure 9*):

- Aortic annular dimensions that lie outside sizing recommendations for currently available transcatheter devices.
- Excessive or bulky calcifications of the annulus or LVOT, which increase the risk of PVL and annular rupture.[424,425]
- Increased risk of coronary obstruction with TAVI (cusp height greater than coronary height in combination with shallow sinuses of Valsalva, or high calcium burden of corresponding cusp).[329]

In contrast, anatomical findings such as porcelain aorta, severe chest deformation, or intact grafts post-CABG favour TAVI. Right anterior thoracotomy or upper hemisternotomy are minimally invasive access alternatives to sternotomy for performing SAVR, which are being used with increasing frequency.[426,427]

In BAV patients, severe AS usually occurs earlier compared with tricuspid AV and is frequently associated with aortopathy.[219,281,428] Prevalence of BAV anatomy sharply increases in younger AS patients.[429] BAV anatomy adds complexity to TAVI because of asymmetric AV calcification and elliptical annular shape, as well as the lack of standardization of valve sizing.

Patients with BAV have been excluded from almost all landmark RCTs comparing TAVI with SAVR to date.[429,430] In the NOTION 2 trial, the composite of all-cause death, stroke, or valve- or HF-related rehospitalization was numerically more frequent (seven vs two events) at 1 year in the underpowered subgroup of 100 patients with BAV (HR, 3.8; 95% CI, 0.8–18.5; $P = 0.07$).[416] Whereas some observational studies report favourable outcomes with TAVI in selected BAV patients,[430–432] others suggest higher stroke, annular rupture, and PVL rates as compared with TAVI in tricuspid AS.[433] Heavy cusp calcification, particularly in conjunction with a calcified raphe, is associated with increased risk of aortic root injury, PVL, and mortality after TAVI.[434] Data on TAVI in two-sinus BAV (Sievers type 0) are scarce.[219,435]

For the above-mentioned reasons, SAVR remains the primary mode of treatment for stenotic BAV, particularly if patients are young or have coexistent aortopathy or unfavourable valve morphology. TAVI may be considered in patients at increased surgical risk, if anatomy is suitable.

Patients with small annuli in relation to their body stature are at increased risk of prosthesis–patient mismatch (PPM) after valve replacement. Annular enlargement allows for implantation of larger BHVs with SAVR. Given its technical complexity it should be performed in experienced centres, and the benefit must be balanced against a possibly higher risk of operative mortality.[436] Prostheses with supra-annular design reduce PPM risk with TAVI, although randomized long-term data evaluating the impact on clinical outcomes or valve durability are pending.[394,437,438]

8.5.1.3. Lifetime management

Decision-making concerning the mode of intervention and type of prosthesis needs to integrate expected valve durability, and the potential risks of future reinterventions (*Figure 9*). Surgical THV explantation followed by SAVR is a rare (<1% of all TAVI procedures) but technically challenging procedure.[439–441] Although its incidence among patients undergoing TAVI is stable, absolute numbers are increasing due to the total increase in TAVI procedures performed and the perioperative risk remains high (early mortality rates as high as 12%–17%).[440–445] The majority of surgical THV explantations are performed in patients at high surgical risk with urgent or emergent, non-SVD-related indication for reintervention (frequently endocarditis) within 2 years after TAVI.[440,442–444]

Implanting a transcatheter aortic valve inside a surgical (TAV-in-SAV) or prior transcatheter valve (TAV-in-TAV) is associated with lower peri-procedural risk compared with redo SAVR.[446–451] However, valve-in-valve implantation (particularly TAV-in-SAV) increases the risk of severe PPM,[448] which has been linked to adverse outcomes in observational studies.[452–455] In addition, valve-in-valve implantation immobilizes the leaflets of the failed prosthesis in an open position, creating a covered tube (or neo-skirt) that may cause direct coronary obstruction in patients with shallow sinuses of Valsalva or indirect

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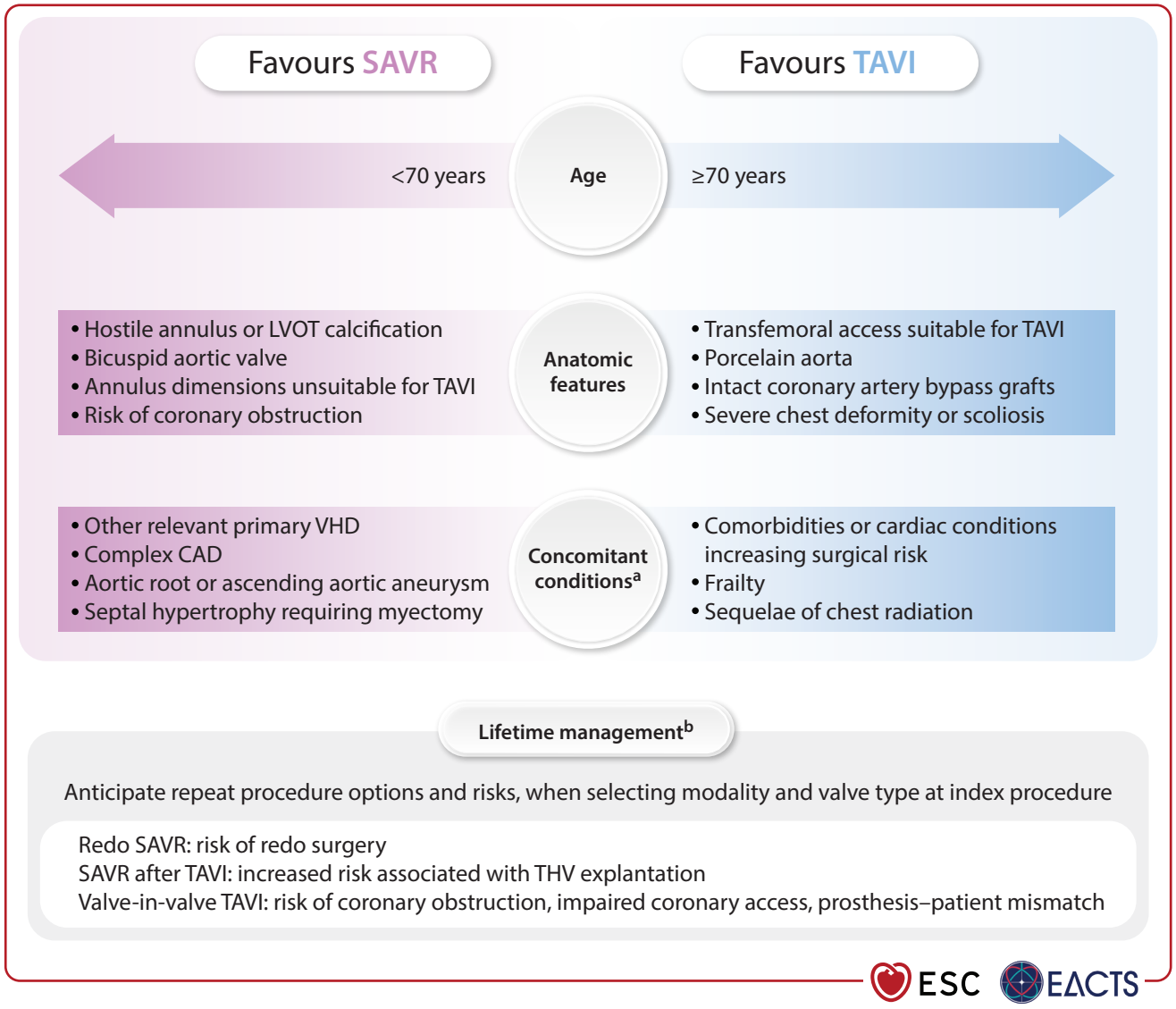
Favours SAVR
Favours TAVI
<70 years
Age
≥70 years
• Hostile annulus or LVOT calcification
• Bicuspid aortic valve
• Annulus dimensions unsuitable for TAVI
• Risk of coronary obstruction
Anatomic features
• Transfemoral access suitable for TAVI
• Porcelain aorta
• Intact coronary artery bypass grafts
• Severe chest deformity or scoliosis
• Other relevant primary VHD
• Complex CAD
• Aortic root or ascending aortic aneurysm
• Septal hypertrophy requiring myectomy
Concomitant conditions[a]
• Comorbidities or cardiac conditions increasing surgical risk
• Frailty
• Sequelae of chest radiation
Lifetime management[b]
Anticipate repeat procedure options and risks, when selecting modality and valve type at index procedure
Redo SAVR: risk of redo surgery
SAVR after TAVI: increased risk associated with THV explantation
Valve-in-valve TAVI: risk of coronary obstruction, impaired coronary access, prosthesis–patient mismatch
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Figure 9 Factors to be considered when selecting the mode of intervention for aortic stenosis. CAD, coronary artery disease; LV, left ventricular; LVOT, left ventricular outflow tract; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve; VHD, valvular heart disease. [a]LV thrombus and infective endocarditis are relative contraindications to TAVI and are therefore not listed. [b]Particularly relevant for patients in whom the anticipated life expectancy is thought to exceed valve durability.

coronary flow obstruction as a result of sinus sequestration if the ascending aorta is narrow and the neo-skirt reaches the sinotubular junction.[456,457]

The risk of coronary obstruction varies considerably depending on the index valve type, and is particularly increased if a stentless SAV or stented SAV with externally mounted leaflets is in place.[457] The risk of sinus sequestration at the time of TAV-in-TAV implantation is particularly increased in supra-annular valves with a high neo-skirt.[458,459] Even if coronary flow is preserved, coronary access may be difficult or impossible in a relevant proportion of patients after valve-in-valve implantation, especially after TAV-in-TAV.[460–462]

In patients who require a reintervention due to dysfunction of a surgical or transcatheter bioprosthesis, but are at increased risk of severe PPM or coronary obstruction, redo SAVR may be preferable despite the increased surgical risk. Fracture of surgical valves and leaflet modification techniques have been proposed for patients at high surgical risk and, if contemplated, should be performed in carefully selected patients at experienced centres (*Table 6*).[463,464]

The need for a meticulous CT-based anatomical analysis is paramount in patients with an estimated life expectancy exceeding the assumed valve durability to anticipate future risks at the time of the index valve intervention. Based on individual assessment, the following measures should be considered with respect to lifetime management:

- Use of surgical and transcatheter valves with proven long-term durability to reduce the likelihood of reintervention.[2,4,375,410,411,465–467]
- SAVR with aortic root enlargement or implantation of a supra-annular transcatheter valve in patients with a small annulus at risk of severe PPM based on the predicted effective orifice area (EOA).[436,438,468,469]
- No implantation of stentless prostheses or prostheses with externally mounted leaflets in patients at risk of coronary obstruction during future TAV-in-SAV implantation.[457]

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- Anticipation of the feasibility and risks of a possible future TAV-in-TAV procedure considering related technical aspects at the index TAVI (device choice, neo-skirt height, commissural alignment, and implantation depth).[456,470]

Considering life-time management aspects and the scarcity of randomized data in patients younger than 70 years, SAVR remains the preferred treatment in patients <70 years of age if surgical risk is low. TAVI is recommended as the primary treatment modality in elderly patients ≥70 years of age with a tricuspid AV, if anatomy is suitable and transfemoral access is feasible, to reduce the risk of early adverse outcomes and accelerate recovery.

For all other candidates for a bioprosthesis, the most appropriate mode of intervention should be carefully selected by the Heart Team, taking into account procedural risk based on anatomical characteristics and comorbidities, expected outcomes, lifetime management considerations, and patient preference (*Figure 9*; *Recommendation Table 4*). Recommendations for concomitant valve replacement at the time of CABG or ascending aortic surgery are listed in *Recommendation Table 5*.

Recommendation Table 4 — Recommendations on indications for intervention in symptomatic and asymptomatic severe aortic stenosis, and recommended mode of intervention (see also Supplementary data online, *Evidence Tables 9–13*)

Recommendations	Class[a]	Level[b]
Symptomatic patients with severe aortic stenosis		
Intervention is recommended in symptomatic patients with severe, high-gradient AS [mean gradient ≥40 mmHg, V_{max} ≥4.0 m/s, AVA ≤1.0 cm^2 (or ≤0.6 cm^2/m^2 BSA)].[388,471–474]	I	B
Intervention is recommended in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with reduced LVEF (<50%) after careful confirmation that AS is severe.[342,345,346,348,475]	I	B
Intervention should be considered in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with normal LVEF (≥50%) after careful confirmation that AS is severe.[c] [293,348,349,476–481]	IIa	B
Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe AS and LVEF <50% without another cause.[14,354–359]	I	B
Intervention should be considered in asymptomatic patients (confirmed by a normal exercise test, if feasible) with severe, high-gradient AS and LVEF ≥50% as an alternative to close active surveillance, if the procedural risk is low.[360–363,367,368]	IIa	A
Intervention should be considered in asymptomatic patients with severe AS and LVEF ≥50% if the procedural risk is low and one of the following parameters is present: • Very severe AS (mean gradient ≥60 mmHg or V_{max} >5.0 m/s).[14,362,363,482–484] • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year.[303,353,364] • Markedly elevated BNP/NT-proBNP levels (more than three times age- and sex-corrected normal range, confirmed on repeated measurement without other explanation).[97,365] • LVEF <55% without another cause.[14,354,356–359]	IIa	B
Intervention should be considered in asymptomatic patients with severe AS and a sustained fall in BP (>20 mmHg) during exercise testing.	IIa	C
Mode of intervention		
It is recommended that AV interventions are performed in Heart Valve Centres that report their local expertise and outcome data, have on-site interventional cardiology and cardiac surgical programmes, and a structured collaborative Heart Team.	I	C
It is recommended that the mode of intervention is based on Heart Team assessment of individual clinical, anatomical, and procedural characteristics, incorporating lifetime management considerations and estimated life expectancy.	I	C
TAVI is recommended in patients ≥70 years of age with tricuspid AV stenosis, if the anatomy is suitable.[d] [1–4,389–397,465,485,486]	I	A
SAVR is recommended in patients <70 years of age, if the surgical risk is low.[e] [413,429,487]	I	B
SAVR or TAVI are recommended for all remaining candidates for an aortic BHV according to Heart Team assessment.[2,4,396,397,429,488–490]	I	B
Non-transfemoral TAVI should be considered in patients who are unsuitable for surgery and transfemoral access.[417–423,491–498]	IIa	B
TAVI may be considered for the treatment of severe BAV stenosis in patients at increased surgical risk, if the anatomy is suitable.[430–432,434,499–502]	IIb	B
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients, and (if feasible) in those with severe AS who require urgent high-risk NCS.	IIb	C

AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; BAV, bicuspid aortic valve; BHV, biological heart valve; BNP, brain natriuretic peptide; BP, blood pressure; BSA, body surface area; CCT, cardiac computed tomography; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; NCS, non-cardiac surgery; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; SVi, stroke volume index; TAVI, transcatheter aortic valve implantation; V_{max}, peak transvalvular velocity.

[a]Class of recommendation.

[b]Level of evidence.

[c]Explanations (such as measurement errors, uncontrolled blood pressure, and conditions lowering the stroke volume) other than severe AS for a small AVA but low gradient despite preserved LVEF are frequent and must be carefully excluded.

[d]Suitability regarding transfemoral access, annulus dimensions, device landing zone calcification pattern, and coronary obstruction risk (*Figure 9*).

[e]Surgical risk based on STS-PROM (http://riskcalc.sts.org/stswebriskcalc/#/calculate) and EuroSCORE II (http://www.euroscore.org/calc.html) <4% and Heart Team assessment.

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Recommendation Table 5 — Recommendations on indications for concomitant aortic valve replacement at the time of coronary artery bypass grafting or ascending aorta surgery

Recommendations	Class[a]	Level[b]
SAVR is recommended in symptomatic and asymptomatic patients with severe AS undergoing CABG or surgical intervention on the ascending aorta.	I	C
SAVR should be considered in symptomatic and asymptomatic patients with moderate AS[c] undergoing CABG or surgical intervention on the ascending aorta.	IIa	C

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AS, aortic stenosis; AVA, aortic valve area; CABG, coronary artery bypass grafting; SAVR, surgical aortic valve replacement.
[a]Class of recommendation.
[b]Level of evidence.
[c]Defined as an AVA of 1.0–1.5 cm^2 (or mean aortic gradient of 25–40 mmHg) in normal-flow conditions. Clinical assessment is essential to determine whether SAVR is appropriate for an individual patient.

8.6. Follow-up

The rate of progression of AS varies widely and asymptomatic patients, their family, and medical caregivers need careful education, with particular emphasis on the importance of regular follow-up (ideally at a Heart Valve Centre)[14] and prompt reporting of symptoms. Asymptomatic patients with severe AS should be followed up at least every 6 months to allow detection of early symptoms (using exercise testing if complaints are inconclusive) and any change in echocardiographic parameters (particularly LVEF). Serial measurements of natriuretic peptides can provide additional useful information regarding the timing of treatment.

Younger patients with mild AS and no significant leaflet calcification may be followed up every 2–3 years. With increasing stenosis severity, progression accelerates and follow-up intervals should be gradually reduced.[283,503] Several studies suggest that the prognosis of moderate degenerative AS is worse than previously considered,[504,505] particularly if there is significant valve calcification, and these patients should be re-evaluated at least annually.

Cardiac rehabilitation is frequently performed after AV intervention, especially after surgery and in elderly patients, and is associated with improved activities of daily living and 6-minute walking distance.[506] After valve intervention, an early echocardiographic examination within the first weeks after valve replacement is recommended to document baseline prosthetic valve function. Cardiological evaluations and echocardiographic examinations are recommended annually in patients with a bioprosthesis, and whenever changes in clinical symptoms or signs suggestive of valve dysfunction are noted.

9. Mitral regurgitation

Chronic MR is one of the most common acquired valve pathologies,[12,187] while acute MR is observed in the context of infective endocarditis, chordal rupture, or as a complication of myocardial infarction (papillary muscle rupture). MR either relates to anatomical changes of the MV apparatus (primary), or to LV or LA dilatation and dysfunction (secondary).[193] Since natural history, prognosis, and management differ according to aetiologies, populations should be clearly distinguished in clinical practice and research.[12,507]

9.1. Primary mitral regurgitation

9.1.1. Prevalence and aetiology

Primary mitral regurgitation relates to an anatomical lesion of one or more of the three main components (not including the annulus) of the MV apparatus (valve leaflets, chordae tendineae, and papillary muscles). PMR is observed in 55% of patients with MR who require treatment.[507] While degenerative disease related to fibroelastic deficiency or myxomatous alterations (in its most severe form, Barlow's disease) are the most common aetiologies in higher-income countries, RHD is most frequently found in the rest of the world. MV endocarditis is a separate entity of PMR caused by acute or chronic infectious conditions and is discussed in the corresponding Guidelines.[5] In a small subgroup of patients, PMR is associated with a higher incidence of ventricular arrhythmias, and sudden cardiac death has been reported in individual cases, especially in patients with Barlow's disease.[508] The arrhythmogenic burden is independent from MR severity and has been associated with mitral annular disjunction. Atrial displacement of the posterior MV leaflet hinge point is assumed to cause excessive mobility of the valvular apparatus and increases tension on the papillary muscles and the posterobasal myocardium, causing local fibrosis, which may lead to ventricular arrhythmias and sudden cardiac death.[509]

9.1.2. Evaluation

9.1.2.1. Echocardiography and right heart catheterization

Echocardiography is the diagnostic method of choice for the quantification of MR, determination of its aetiology, and identification of cardiac consequences (*Figure 10*). TTE is used for initial evaluation that includes: (i) assessment of valve morphology (presence and location of prolapse or flail, calcifications, and/or mitral annular disjunction); (ii) integrative severity grading; and (iii) quantification of LV and LA dimensions and function, as well as assessment of concomitant RV dysfunction.[46] Quantitative parameters such as the effective regurgitant orifice area (EROA) have prognostic implications.[510,511] Volumetric methods provide additional information on MR severity [RVol and regurgitant fraction (RF)].[512] Accurate colour flow settings must be used to avoid overestimation of MR severity.

Transoesophageal echocardiography (TOE) represents the method of choice to assess valve anatomy, leaflet quality, motion, and coaptation, as well as to confirm MR severity.[513] Three-dimensional TOE provides an excellent morphological and functional view of the different valve segments, and should be used systematically when planning and performing surgical or transcatheter repair.[514]

Exercise echocardiography evaluates dynamic changes in regurgitant jet and pulmonary pressures during peak exercise, and might be helpful in patients with discordant symptoms and regurgitation severity at rest.[515,516]

In asymptomatic patients with severe PMR, increased LV or LA dimensions, as well as elevated pulmonary pressures (>50 mmHg at rest), moderate or more secondary TR, and AF are important markers of worse prognosis, and should be considered for intervention timing (*Figure 11*; *Section 9.1.4*).[517,518]

Right heart catheterization remains important in patients with PMR for confirmation of pulmonary artery pressures in case of discrepancy between echocardiographic MR severity and clinical symptoms, as well as in the presence of concomitant lung disease.[519]

9.1.2.2. Biomarkers

Cardiac biomarkers are recognized indicators of disease severity with prognostic implications, but may also be non-specific. NT-proBNP levels are directly related to the New York Heart Association (NYHA) functional class in PMR.[520]

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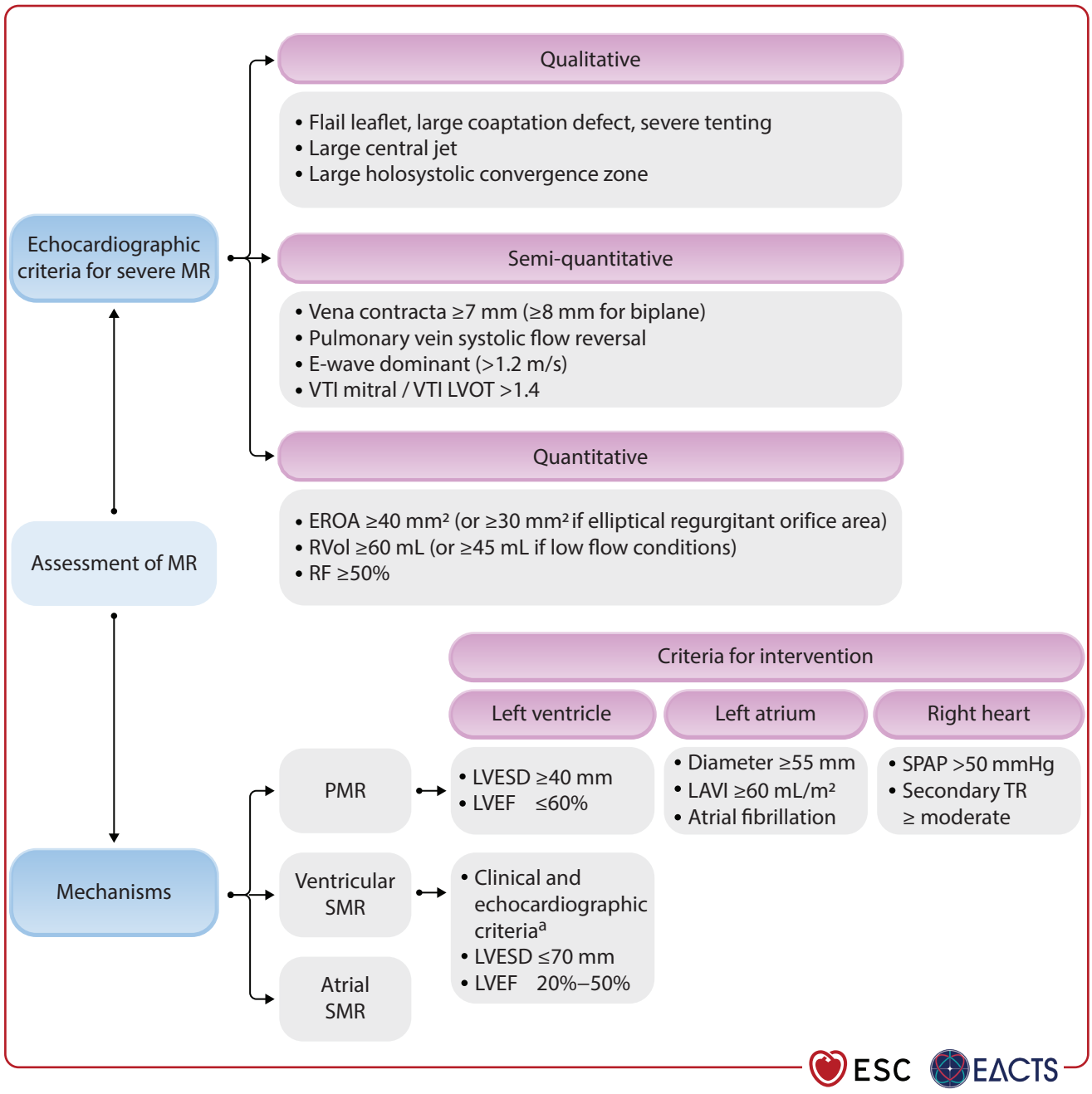

Figure 10 Echocardiographic assessment of patients with mitral regurgitation. EROA, effective regurgitant orifice area; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVOT, left ventricular outflow tract; MR, mitral regurgitation; PMR, primary mitral regurgitation; RF, regurgitant fraction; RVol, regurgitant volume; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; VTI, velocity time integral. [a]See *Table 7* for criteria predicting outcome improvement.

In a multicentre registry including more than 1300 patients with PMR, increased BNP level was an independent predictor of long-term mortality under medical treatment. However, pre-operative BNP activation did not impact long-term mortality after surgical treatment.[96]

9.1.2.3. Cardiac magnetic resonance and computed tomography

Cardiac magnetic resonance imaging is an alternative to precisely quantify RVol and RF in cases of inconclusive or discordant measurements, and the gold standard to determine cardiac dimensions and chamber volumes.[521,522] The combination of planimetered volumetric methods and phase contrast measurement of the MV inflow are used for this purpose.[523] In patients with Barlow's disease and mitral annular disjunction, CMR-detected myocardial fibrosis[524] has been associated with ventricular arrhythmias and sudden cardiac death.[525]

Cardiac computed tomography provides high-resolution anatomical details of the entire MV apparatus[523,526] and increasingly plays a role in MV intervention planning, particularly in the assessment of arterial access for extracorporeal circulation and the presence of MV calcification in minimally invasive surgery,[527] as well as the feasibility of transcatheter MV implantation (TMVI) based on annulus size and risk of LVOT obstruction.[528]

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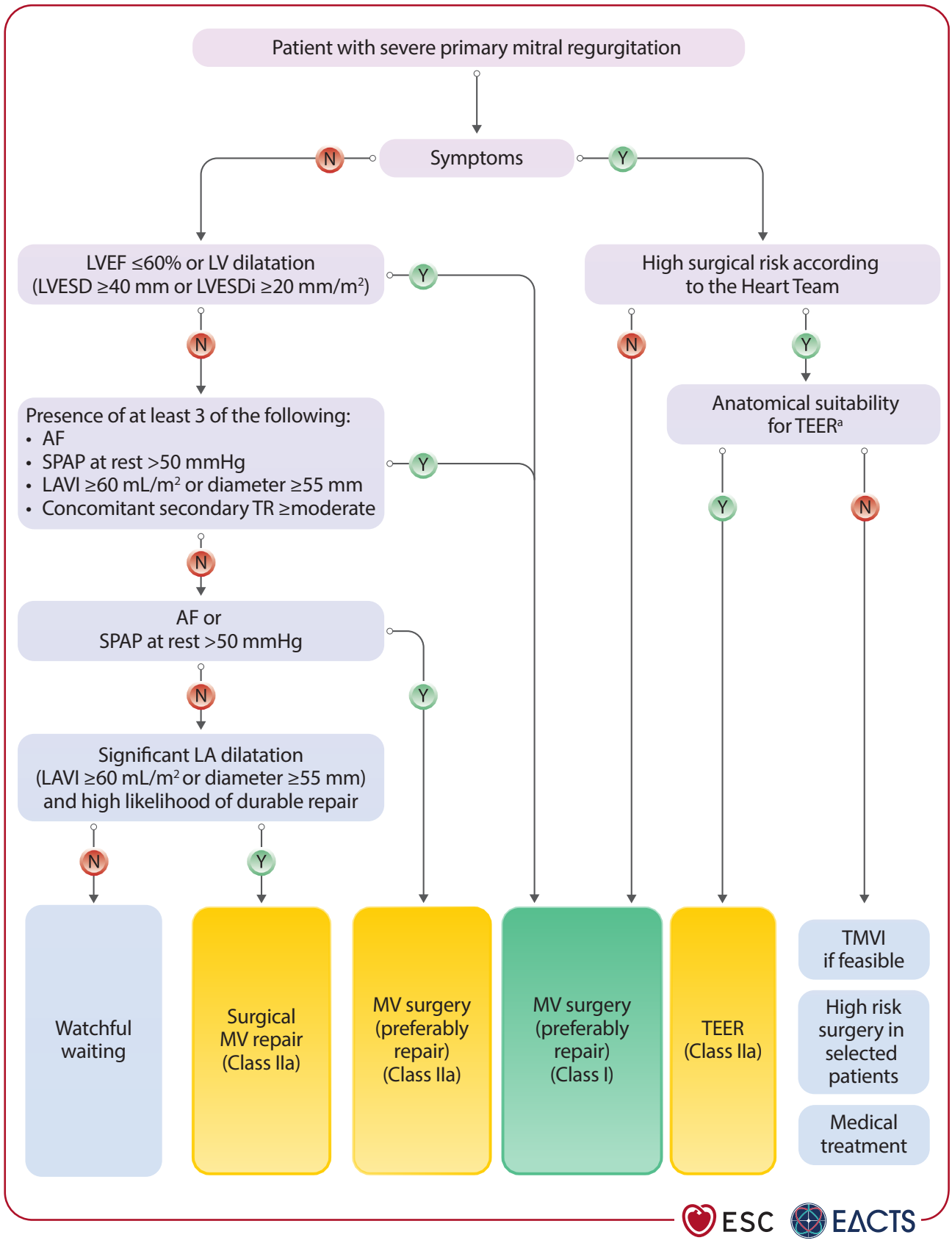

Figure 11 Management of patients with severe primary mitral regurgitation. AF, atrial fibrillation; LA, left atrial; LAVI, left atrial volume index; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to BSA; MV, mitral valve; SPAP, systolic pulmonary artery pressure; TEER, transcatheter edge-to-edge repair; TMVI, transcatheter mitral valve implantation; TR, tricuspid regurgitation. [a]See Supplementary data online, *Table S2*.

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Due its high sensitivity for detection of calcifications, CCT is instrumental for procedural planning (surgical and transcatheter) in patients with MAC.[529]

9.1.2.4. Genetic evaluation

There is increasing evidence that specific mitral pathologies may be associated with genetic conditions. A meta-analysis of six genome-wide association studies identified 14 potential genetic loci associated with primary MR. By comprising epigenetic, transcriptional, and proteomic data, the following genes could be identified as potential genetic sources of the pathology: *LMCD1*, *SPTBN1*, *LTBP2*, *TGFB2*, *NMB*, and *ALPK3*.[530] However, genetic testing is not recommended in routine practice.

9.1.3. Medical therapy

Medical therapy has a limited role in patients with PMR. Afterload reduction with sodium nitroprusside has been used as a bridge to an intervention in patients with acute severe PMR without signs of hypotension. Inotropic agents and diuretics are usually indicated to reduce filling pressures and control pulmonary congestion, while the implantation of an intra-aortic balloon pump helps to further reduce afterload in exceptional cases of acute PMR.

In chronic PMR without signs of LV dysfunction or criteria for an intervention, there is no evidence supporting prophylactic afterload reduction. Patients with PMR and impaired LV function should receive GDMT according to HF Guidelines.[340]

9.1.4. Indications for intervention

Urgent surgery or transcatheter treatment is indicated in patients with acute severe PMR because it is poorly haemodynamically tolerated. In patients with papillary muscle rupture and endocarditis, surgical valve replacement is generally required, while acute degenerative chordal rupture can be treated with surgical MV repair or TEER in high-risk patients.

Indications for surgery in patients with chronic asymptomatic and symptomatic PMR are summarized in *Recommendation Table 6* and *Figure 11*. In cases of severe PMR, restoring the anatomy by surgical MV repair, including annuloplasty, is the treatment of choice in operable patients when an optimal and durable result is expected. According to contemporary data, the procedure can be performed with a low mortality risk (1.2%) in appropriately selected patients.[531] Compared with replacement, MV repair has been associated with lower peri-operative mortality along with significantly better long-term survival and functional outcomes.[532,533] Repair of more complex pathologies such as valves with annular or leaflet calcifications, as well as in cases of RHD, is challenging and should be attempted in experienced Heart Valve Centres.[534–536] When MV repair is not feasible, valve replacement with preservation of the subvalvular apparatus should be performed.[537]

High-risk and elderly patients with chronic PMR, though uncommon, may benefit from a less-invasive M-TEER procedure.[538] Peri-interventional and mid-term results with regard to residual MR and mean transmitral gradient are closely related to patient outcomes.[538] The use of latest-generation devices along with a growing team experience have improved results, and allow for the successful treatment of more complex anatomical conditions (Supplementary data online, *Table S2*).[539,540] The decision regarding the mode of intervention or conservative treatment should be made by the Heart Team, considering clinical and anatomical characteristics, as well as procedural risks and patient preference. The longer-term efficacy of TEER compared with surgery is still under investigation in high- (NCT03271762) and intermediate-risk PMR patients (NCT04198870), as well as in all-risk-category patients >60 years of age (NCT05051033).[541] TMVI is very effective in abolishing MR in selected high-risk patients, particularly those with complex MV anatomy for TEER (Supplementary data online, *Table S2*).[542,543] The major drawbacks of current TMVI systems include limited availability, high screening failure rate, as well as the risk of LVOT obstruction and valve thrombosis. Limited data exist for PMR patients and regarding mid-term prosthesis durability.

In patients with asymptomatic PMR with signs of LV dysfunction (i.e. LVEF ≤60%, LVESD ≥40 mm, or LVESDi ≥20 mm/m^2) the benefit of early surgery is well established.[544–546] Furthermore, there is increasing evidence that the presence of LA dilatation [LA volume index (LAVI) ≥60 mL/m^2 or LA diameter ≥55 mm], AF, systolic pulmonary artery pressure (SPAP) at rest of >50 mmHg, and concomitant moderate or severe secondary TR are associated with worse long-term prognosis irrespective of LV function after corrective surgery, and should therefore prompt referral in low-risk patients, particularly if a high probability of MV repair is expected.[517,518,547] A recent study showed that women have a higher risk of long-term mortality after MV repair than men, even at lower degrees of ventricular dilatation and dysfunction, suggesting the potential usefulness of sex-specific indexed thresholds.[548] Ventricular arrhythmias in patients with MV prolapse have been linked to impaired prognosis and possibly sudden cardiac death, especially in the presence of mitral annular disjunction.[549–551] Ring annuloplasty stabilizes the posterior annulus, reduces traction on the subvalvular apparatus,[552] and may lower the risk of arrhythmias.[553] Minimally invasive surgery via right mini-thoracotomy is used with increasing frequency in experienced centres.[554–556] A recent RCT demonstrated similar safety and efficacy compared with conventional sternotomy. Mini-thoracotomy was associated with shorter hospital stay and improved physical activity within the first 6 weeks after surgery, a difference that disappeared at 12 weeks.[557] The use of minimally invasive MV surgery may therefore be considered to reduce hospital stay and accelerate recovery in experienced centres. However, in a national registry, these benefits were less clear.[558]

Recommendation Table 6 — Recommendations on indications for intervention in severe primary mitral regurgitation (see also Supplementary data online, *Evidence Tables 14–16*)

Recommendations	Class[a]	Level[b]
MV repair is the recommended surgical technique to treat patients with severe PMR when the result is expected to be durable.[26,532,533,559,560]	I	B
MV surgery is recommended in symptomatic patients with severe PMR considered operable by the Heart Team.[26,532,533,561]	I	B
MV surgery is recommended in asymptomatic patients with severe PMR and LV dysfunction (LVESD ≥40 mm or LVESDi ≥20 mm/m^2 or LVEF ≤60%).[522,544,545]	I	B

Continued

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Surgical MV repair is recommended in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) when a durable result is likely, if at least three of the following criteria are fulfilled:[517,547,562–564] • AF • SPAP at rest >50 mmHg • LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm) • Concomitant secondary TR ≥ moderate.	I	B
MV surgery should be considered in asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) in the presence of PH (SPAP at rest >50 mmHg), or AF secondary to MR.[517,518,562,565]	IIa	B
Surgical MV repair should be considered in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) in the presence of significant LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm), when performed in a Heart Valve Centre and a durable repair is likely.[517,565]	IIa	B
TEER should be considered in symptomatic patients with severe PMR who are anatomically suitable and at high surgical risk according to the Heart Team.[538,540,566]	IIa	B
Minimally invasive MV surgery may be considered at experienced centres to reduce the length of stay and accelerate recovery.[557,567]	IIb	B

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AF, atrial fibrillation; LA, left atrium/left atrial; LAVI, left atrial volume index; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to body surface area; MR, mitral regurgitation; MV, mitral valve; PH, pulmonary hypertension; PMR, primary mitral regurgitation; SPAP, systolic pulmonary artery pressure; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation.
[a]Class of recommendation.
[b]Level of evidence.

9.1.5. Follow-up

Asymptomatic patients with severe MR not fulfilling the criteria for an intervention, and with documented preserved exercise capacity, should undergo clinical and echocardiographic follow-up twice per year (watchful waiting strategy), ideally in the setting of a Heart Valve Clinic.[568] Follow-up may also include serial measurements of BNP levels, electrocardiogram (ECG) and/or Holter monitoring, and (in selected cases) exercise echocardiography and CMR to confirm MR severity, and cardiac chamber function and dimensions.[46] Asymptomatic patients with moderate MR and preserved LV function can be followed on a yearly basis with echocardiographic assessment every 1 or 2 years.

The frequency of follow-up after an intervention depends on the type of procedure performed. Very good long-term durability of MV repair in PMR due to valve prolapse with a low recurrence rate has been reported at experienced centres with freedom from moderate or severe MR of 87.5% at 20 years.[533,559] Serial clinical and echocardiographic follow-up in patients without pre-operative LV dysfunction or rhythm abnormalities every 2–3 years thereafter is sufficient. Patients with atrial or ventricular arrhythmias possibly related to MV disease should be further evaluated using continuous ECG monitoring. Patients with recurrent MR after surgical ring annuloplasty frequently undergo repeat surgery (usually MV replacement), while transcatheter alternatives are reserved for selected high-risk patients because of the risk of increased gradients (M-TEER), PVL, and LVOT obstruction (mitral valve-in-ring procedures).[569,570] In patients undergoing MV replacement, closer follow-up on a yearly basis is required due to the risk of prosthetic valve dysfunction or SVD (see *Section 14.4*). Following TEER, reported rates of residual MR and increased transmitral gradients are higher than after surgical repair, suggesting that yearly follow-up is appropriate.[571] Although rare, the need for surgical treatment after failed TEER is associated with increased peri-operative mortality and low valve repair rates,[541,572] while transcatheter solutions to detach TEER implants and replace the valve have been described in few cases.[573,574]

9.2. Secondary mitral regurgitation

9.2.1. Prevalence and aetiology

Secondary mitral regurgitation is present when the MV structure appears grossly normal but the MV is nonetheless incompetent, due to alterations in LV and LA geometry, dyssynchrony, and imbalances between MV closing and tethering forces.[575] The prevalence of severe SMR in patients with chronic HF is ~10% and higher in patients with reduced vs preserved LVEF (25% vs 4%).[576] Secondary mitral regurgitation can be classified as atrial or ventricular with different pathophysiological and morphological characteristics, as well as contrasting prognostic and therapeutic implications.[577] Ventricular SMR is more common and associated with worse long-term prognosis.[513,578–580] Dilated or ischaemic cardiomyopathy are the most frequent causes of severe ventricular SMR. Acute HF exacerbation may occur in patients with chronic HF due to a renewed ischaemic event, arrhythmia, infection, or volume overload. Atrial SMR is due to pure mitral annular dilation and is observed in patients with long-standing AF and/or HFpEF.[581] Factors predisposing to atrial SMR include age ≥65 years, female sex, LA dilatation, and diastolic dysfunction.[582] From a morphological point of view, ventricular SMR is characterized by leaflet tethering and restricted motion combined with annular dilation, while annulus enlargement and flattening leading to planar coaptation are predominantly observed in atrial SMR. The prevalence of atrial SMR has been underestimated in the past and was occasionally misclassified as PMR due to pseudo-prolapse with leaflet tethering in advanced stages.

9.2.2. Evaluation

Echocardiographic criteria to define significant SMR according to aetiology are reported in *Figure 10*. Importantly, SMR assessment should be performed after optimization of medical therapy and in a euvolaemic and normotensive state. When quantifying EROA and RVol in SMR, lower thresholds may apply to define severe regurgitation because of the potential elliptical regurgitant orifice and/or the low-flow state. An EROA of ≥30 mm^2 and/or an RVol of ≥45 mL has been identified as having a significant impact on outcomes,[45] with prognosis improved after treatment.[583,584] Cardiac magnetic resonance is used to confirm SMR severity and assess cardiac chamber function and dimensions. The extent of myocardial fibrosis, as assessed with CMR, has been associated with poor prognosis.[585] Owing to the dynamic nature of SMR, exercise echocardiography may help to identify patients with severe SMR when values at rest are inconclusive.[45]

9.2.3. Definition of atrial secondary mitral regurgitation

Characteristics distinguishing between atrial and ventricular SMR are displayed in *Figure 12*.

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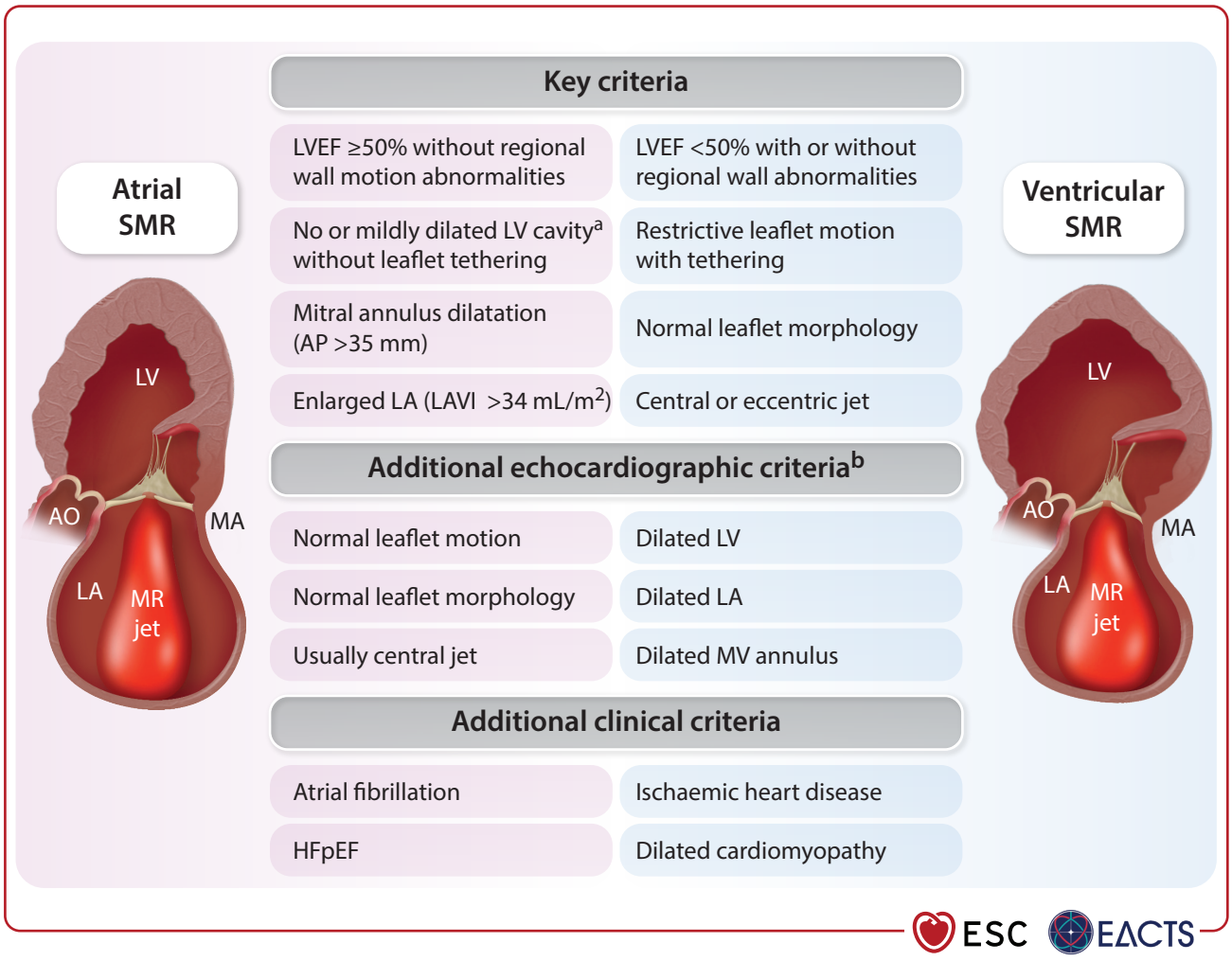

Figure 12 Most frequently used criteria for the diagnosis of atrial secondary mitral regurgitation. AO, aorta; AP, anteroposterior; HFpEF, heart failure with preserved ejection fraction; LA, left atrium/left atrial; LAVI, left atrial volume index; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; MA, mitral annulus; MR, mitral regurgitation; MV, mitral valve; SMR, secondary mitral regurgitation. [a]LV end-diastolic dimension of <56 mm in females and <63 mm in males; indexed LV end-diastolic volume <71 mL/m^2 (in women) or <79 mL/m^2 (in men). [b]Additional echocardiographic criteria for atrial SMR may no longer be fulfilled in advanced stages.

Atrial SMR is most frequently defined by the presence of the following key criteria:[513,578–580,586–590]

- preserved LVEF (≥50%) without regional wall motion abnormalities or leaflet tethering; AND
- no or mildly dilated LV cavity [LV end-diastolic dimension of <56 mm in women and <63 mm in men; indexed LV end-diastolic volume of <71 mL/m^2 (in women) or <79 mL/m^2 (in men)]; AND
- mitral annulus (MA) dilatation [anteroposterior (AP) diameter of >35 mm]; AND
- enlarged LA (LAVI >34 mL/m^2).

Echocardiography frequently reveals normal leaflet motion with planar coaptation, and normal leaflet morphology with a central MR jet in atrial SMR. However, at advanced stages, an overlap between atrial and ventricular SMR criteria can be observed in the case of late LV damage due to continuous volume overload.[591,592] Clinical criteria (i.e. history of AF and/or diagnosis of HFpEF) are also useful and should be taken into consideration.

9.2.4. Management of ventricular secondary mitral regurgitation

9.2.4.1. Medical and device therapy

In patients with ventricular SMR, GDMT for the treatment of HF is recommended prior to any MV intervention.[339,340] The combination of ACE-Is/ARBs or angiotensin receptor/neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose co-transporter 2 inhibitors (SGLT2is) at the maximum tolerated doses is recommended according to the HF Guidelines.[340] Initiation and up-titration of neurohormonal drugs need to be tailored according to the patient profile, mainly based on BP, heart rate, potassium levels, and renal function.[593] Notably, GDMT up-titration must be rapid (within 6 weeks) and take place in the context of close follow-up visits, especially in the case of a recent hospitalization for acute HF.[594] About 40% of patients with ventricular SMR experience improvement of SMR severity after 1–3 months of optimized GDMT.[595,596] Cardiac resynchronization therapy (CRT) should also be considered as part of HF management before an MV intervention according to HF guideline criteria (LVEF ≤35% and wide QRS).[597,598] Although no dedicated RCTs

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exist, SMR reduction by at least one grade has been described in 40%–60% of patients and is associated with reverse LV remodelling and improved clinical outcomes.[597,599,600]

9.2.4.2. Indications for intervention

The management of patients with ventricular SMR should be discussed by a multidisciplinary Heart Team including HF specialists. The indication for intervention is based on the persistence of symptoms (i.e. NYHA class II–V) despite adequate GDMT and CRT, if indicated (*Figure 13*). GDMT is the only option for very frail patients or those with limited life expectancy.

In the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, M-TEER was shown to be safe and reduced recurrent HF hospitalization and all-cause mortality at 2 and 5 years of follow-up, compared with optimized GDMT in patients with ventricular SMR without relevant CAD.[583,584] In a second study (Percutaneous Repair with the MitraClip Device for

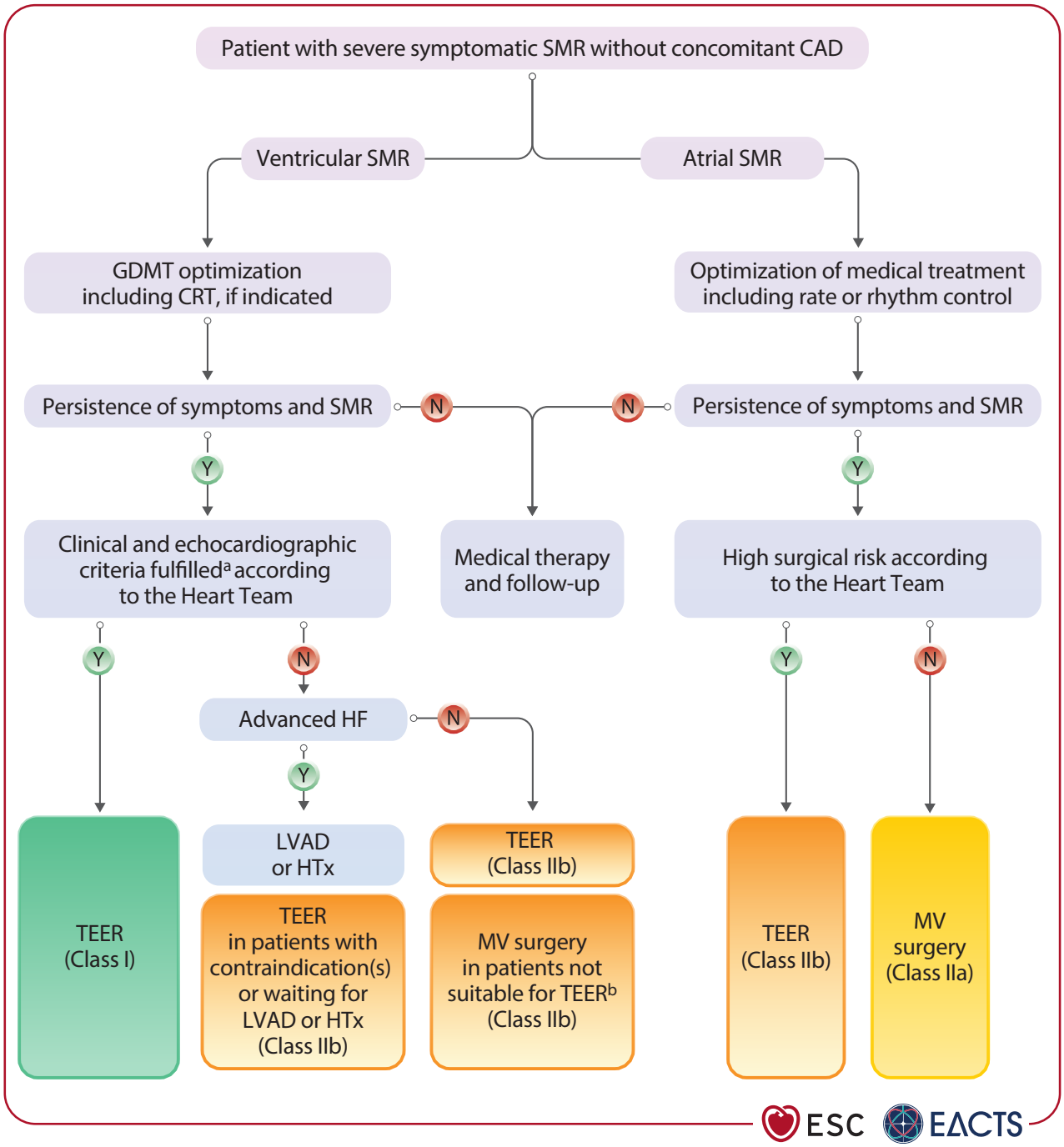

Figure 13 Treatment of severe secondary mitral regurgitation without concomitant coronary artery disease. CAD, coronary artery disease; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HTx, heart transplantation; LVAD, left ventricular assist device; MV, mitral valve; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair. [a]See *Table 7*. [b]See Supplementary data online, *Table S2*.

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Severe Functional/Secondary Mitral Regurgitation, MITRA-FR), no differences were demonstrated for the combined primary endpoint of all-cause mortality or HF hospitalization at 1 and 2 years.[601,602] These diverging results might be explained by effect sizes of the trials, differences in trial design, patient selection and follow-up, echocardiographic assessment of SMR severity, use of GDMT, and technical factors.[603–605] A third RCT, the Randomized Investigation of the MitraClip Device in Heart Failure: 2nd Trial in Patients with Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF-2) trial showed a 36% reduction in the rates of HF hospitalization or cardiovascular death at 2 years in the intervention arm driven by reduction of first or recurrent HF hospitalization. When considered in isolation, cardiovascular mortality was not significantly reduced during the observation period. In addition, there was a significant improvement in quality of life as measured by the KCCQ overall score (mean difference between study groups, 10.9 points; 95% CI, 6.8–15.0; P <0.001).[606] A recent study-level meta-analysis of these three trials showed a significant reduction of HF rehospitalization at 24 months (HR, 0.63, 95% CI, 0.50–0.80) and the composite of death and all-cause hospitalizations (HR, 0.72, 95% CI, 0.51–0.999).[607] However, there was no statistically significant difference in death from any cause or cardiovascular death at 24 months. Transcatheter edge-to-edge repair is therefore recommended to reduce HF hospitalizations, and improve quality of life, in symptomatic patients with persisting severe SMR despite optimized GDMT fulfilling specific clinical and echocardiographic criteria (*Table 7*). Although less challenging than in PMR, anatomical suitability for TEER needs to be assessed upfront (Supplementary data online, *Table S2*). There is also increasing observational evidence supporting the use of TEER for the improvement of symptoms, functional capacity, and quality of life in patients with ventricular SMR not fulfilling the clinical and echocardiographic criteria for outcome improvement.[608–612] This particularly applies to patients not tolerating GDMT in whom TEER may help up-titration, as well as those with recent myocardial infarction and persistent severe ventricular SMR.[203,613]

Transcatheter implantation of an indirect annuloplasty device into the coronary sinus has been proposed as an alternative that preserves valve integrity. Despite rather modest SMR reduction (22.4% decrease in mitral RVol) and no significant effect on quality of life in a small sham-controlled RCT, symptomatic improvement and reverse remodelling were observed in registries at 1 year.[614,615] Heart transplantation or left ventricular assist device (LVAD) implantation should be considered in selected patients with severe ventricular SMR and advanced HF.

In patients with ventricular SMR without relevant CAD, indications for isolated MV surgery are restrictive owing to procedural risks and the absence of proven mortality benefit.[616] The Multicenter, Randomized, Controlled Study to Assess Mitral Valve Reconstruction for Advanced Insufficiency of Functional or Ischemic Origin (MATTERHORN) trial, which included a mixed population mainly composed of patients with ventricular SMR (84%), demonstrated that TEER is non-inferior to surgical repair or replacement with regard to a composite endpoint of death, HF hospitalization, MV reintervention, implantation of an assist device, or stroke within 1 year after the procedure, and showed a better safety profile.[617] In patients with severe ischaemic ventricular SMR and concomitant CAD requiring coronary revascularization, MV surgery at the time of CABG is recommended, unless the patient is at high surgical risk and/or the coronary anatomy is suitable for PCI. Although isolated undersized mitral annuloplasty is the most commonly performed MV repair procedure, recurrent MR rates were high with this technique in an RCT[618] and reverse LV remodelling is limited, especially in patients with an increased tenting area (>1.35 cm^2/m^2 BSA),[619] in whom MV replacement is usually required.[620] The addition of subvalvular modification in patients with LV dilatation and pronounced MV leaflet tenting may improve results for MV repair,[621] but durability and impact on HF symptoms with this technique require further investigation.

The treatment of moderate ischaemic SMR in patients undergoing CABG remains controversial. Meta-analyses, including four RCTs comparing CABG with concomitant MV surgery vs CABG alone, have shown lower rates of recurrent MR but no benefit in terms of mortality and clinical outcomes.[622–624] Therefore, clinical decision-making should weigh peri-operative risks of more complex surgery against the long-term risk of MR progression.

9.2.4.3. Follow-up

Patients with ventricular SMR need to be followed up carefully after intervention by an HF specialist, because they remain at increased risk of events despite intervention. The 5-year cumulative incidence of all-cause death or HF hospitalization was 73.6% in the device arm of the COAPT study.[584] Clinical, laboratory, and echocardiographic evaluation every 3 or 6 months, according to the HF stage, is recommended. Durability of the procedural result, as well as congestion status and the need for further GDMT optimization facilitated by SMR reduction,[613] need to be assessed. Patients and families should be trained in monitoring vital signs, body weight, and HF symptoms to avoid late hospital admissions and facilitate management of possible decompensation. Also, patients must be educated on the importance of not discontinuing medical therapies after intervention since the two treatments (devices and drugs) are complementary.

Patients with ventricular SMR, who are asymptomatic and/or have moderate or dynamic MR, should undergo clinical and echocardiographic follow-up at least twice per year.

Table 7 Clinical and echocardiographic criteria predicting outcome improvement in patients with severe ventricular secondary mitral regurgitation undergoing mitral transcatheter edge-to-edge repair

Anatomy deemed suitable for M-TEER
NYHA class ≥II
LVEF 20%–50%
LVESD ≤70 mm
At least one HF hospitalization within the previous year or increased natriuretic peptide levels (BNP ≥300 pg/mL or NT-proBNP ≥1000 pg/mL)
SPAP ≤70 mmHg
No severe RV dysfunction
No Stage D or advanced HF
No CAD requiring revascularization
No severe AV and/or TV disease
No hypertrophic, restrictive, or infiltrative cardiomyopathies

AV, aortic valve; BNP, brain natriuretic peptide; CAD, coronary artery disease; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; M-TEER, mitral transcatheter edge-to-edge repair; NT-proBNP, N-terminal pro-B-type natriuretic protein; NYHA, New York Heart Association; RV, right ventricle/right ventricular; SPAP, systolic pulmonary artery pressure; TV, tricuspid valve.

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9.2.5. Management of atrial secondary mitral regurgitation

9.2.5.1. Medical therapy and rhythm management

In patients with atrial SMR, underlying causes need to be recognized and treated. Associated HFpEF and AF should be managed according to the relevant Guidelines.[7,340] The use of SGLT2is should be encouraged in patients with HFpEF due to their proven efficacy in reducing cardiovascular death and HF hospitalization.[625] Limited data show that rhythm control may contribute to reduce atrial SMR severity and reverse LA dilatation.[626]

9.2.5.2. Indications for intervention

Registry data demonstrate that patients with atrial SMR are typically elderly with associated AF. Mitral valve surgery has been recently associated with lower rates of HF hospitalizations and mortality compared with GDMT in a matched population, despite a higher risk profile in the surgical arm at baseline.[627] Data from several observational studies also suggest that surgical annuloplasty is effective and durable in patients with atrial SMR, because it counteracts the main mechanism of MR progression.[628–630] Its combination with surgical AF ablation (Maze procedure) and concomitant LAAO may have further advantages,[630,631] while the frequently associated relevant TR can also be addressed during the same procedure.[627] Transcatheter edge-to-edge repair may also be considered because observational studies have demonstrated high safety and procedural success,[588–590,632,633] as well as compared with surgery in a small subgroup ($n = 34$) of the MATTERHORN RCT.[634] However, the risk of increased gradient due to planar leaflet coaptation, large regurgitant jet, and limited MV area (MVA) needs to be taken into consideration.[592,635] Further studies are warranted to investigate the treatment modalities of patients with atrial SMR.

9.2.5.3. Follow-up

Patients with atrial SMR undergoing surgical or transcatheter intervention should be followed up on a yearly basis, including clinical and echocardiographic evaluation. In cases of HFpEF, as an underlying cause of atrial SMR, consultation with an HF specialist is necessary.

Asymptomatic patients with severe atrial SMR not fulfilling the criteria for an intervention should undergo clinical and echocardiographic follow-up at least once per year.

Recommendation Table 7 — Recommendations on indications for intervention in secondary mitral regurgitation (see also Supplementary data online, *Evidence Tables 17–20*)

Recommendations	Class[a]	Level[b]
Severe atrial secondary mitral regurgitation		
MV surgery, surgical AF ablation, if indicated, and LAAO should be considered in symptomatic patients with severe atrial SMR under optimal medical therapy.[627–630,636,637]	IIa	B
TEER may be considered in symptomatic patients with severe atrial SMR not eligible for surgery after optimization of medical therapy including rhythm control, when appropriate.[588,590,638,639]	IIb	B
Ventricular secondary mitral regurgitation and concomitant coronary artery disease		
MV surgery is recommended in patients with severe ventricular SMR undergoing CABG.[640]	I	B
MV surgery may be considered in patients with moderate SMR undergoing CABG.[622–624,641,642]	IIb	B
PCI followed by TEER after re-evaluation of MR may be considered in symptomatic patients with chronic severe ventricular SMR and non-complex CAD.[150]	IIb	C
Severe ventricular secondary mitral regurgitation without concomitant coronary artery disease		
TEER is recommended to reduce HF hospitalizations and improve quality of life in haemodynamically stable, symptomatic patients with impaired LVEF (<50%) and persistent severe ventricular SMR, despite optimized GDMT and CRT (if indicated), fulfilling specific clinical and echocardiographic criteria.[c] [583,584,606,608,643]	I	A
TEER may be considered for symptom improvement in selected symptomatic patients with severe ventricular SMR not fulfilling the specific clinical and echocardiographic criteria,[c] after careful evaluation of LVAD or HTx.[203,608–610]	IIb	B
MV surgery may be considered in symptomatic patients with severe ventricular SMR without advanced HF who are not suitable for TEER.[617]	IIb	C

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HTx, heart transplantation; LAAO, left atrial appendage occlusion; LVAD, left ventricular assist device; LVEF, left ventricular ejection faction; MR, mitral regurgitation; MV, mitral valve; PCI, percutaneous coronary intervention; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Table 7*.

10. Mitral stenosis

10.1. Prevalence and aetiology

The aetiology of MS is most frequently rheumatic or degenerative, while rare forms can be drug-induced, inflammatory, or carcinoid-related. Rheumatic fever is the most common cause of MS and death due to VHD worldwide. Its prevalence has decreased in high- and middle-income countries, but remains a major healthcare problem in low-income countries, where it predominantly affects young patients.[12,187,644] Degenerative MS related to MAC is a distinct age-dependent pathology requiring different treatment strategies.[645–647] Both aetiologies are more frequent in females.[648]

10.2. Rheumatic mitral stenosis

10.2.1. Evaluation

Echocardiography is the preferred method for screening in endemic regions and the assessment of the severity, extent of anatomical lesions, and haemodynamic consequences of MS. Involvement of other valves, particularly secondary TR, should be identified. Mitral valve area using

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2D planimetry is the most commonly used measurement to assess stenosis severity, but 3D TTE and TOE have additional diagnostic value.[649] An MVA of ≤1.5 cm^2 in conjunction with clinical factors (symptoms, high risk of thromboembolism, or haemodynamic decompensation) is indicative of clinically severe MS. Mean transvalvular gradient and pulmonary pressures reflect its consequences and have prognostic value.[649,650] Leaflet thickening and fibrosis, along with commissural fusion and shortening of the subvalvular apparatus, are the most important pathomechanisms of stenosis associated with RHD. The presence and extent of leaflet and subvalvular calcifications influence treatment decisions. Scoring systems have been developed to assess the suitability of patients for percutaneous mitral commissurotomy (PMC) (see Supplementary data online, *Table S3*).[651–653]

Exercise testing is indicated in asymptomatic patients or patients with symptoms that are equivocal or discordant with the severity of stenosis. Exercise echocardiography provides additional information on exercise capacity and related changes in mitral gradient and pulmonary artery pressure, and is preferred over DSE, especially when there are contraindications to dobutamine.[654] Transoesophageal echocardiography should be systematically performed in PMC candidates to exclude LA thrombus or after an embolic episode, and may play an essential role for procedural guidance.[52,655]

10.2.2. Medical therapy

Diuretics, beta-blockers, digoxin, non-dihydropyridine calcium channel blockers, and ivabradine can improve symptoms by controlling volume overload and heart rate. Anticoagulation with a VKA with a target international normalized ratio (INR) between 2 and 3 is indicated in patients with AF, and DOACs should be avoided in patients with an MVA of ≤2.0 cm^2 according to current evidence.[165,656,657] Interventions to restore sinus rhythm (cardioversion or catheter pulmonary vein isolation) are unlikely to be successful in patients with untreated severe MS. If AF is of recent onset and the LA moderately enlarged, cardioversion can be attempted soon after successful intervention or in patients with moderate MS combined with amiodarone treatment.[658,659] In patients in sinus rhythm, OAC is indicated after systemic embolism or if a thrombus is present in the LA, and should also be considered when TOE shows dense spontaneous echocardiographic contrast or an enlarged LA (M-mode diameter >50 mm or LA volume >60 mL/m^2).[660] Prophylaxis of infective endocarditis is indicated as appropriate.[5]

10.2.3. Indications for intervention

The type (PMC or surgery) and timing of treatment should be decided based on clinical characteristics, the anatomy of the valve and subvalvular apparatus, and local expertise.[661–663] The management of clinically severe rheumatic MS is summarized in *Figure 14* and *Recommendation Table 8*.

In general, indication for intervention should be limited to patients with clinically severe rheumatic MS (MVA <1.5 cm^2) in whom PMC is expected to have a significant impact on clinical outcome. In higher-income countries, where the incidence of rheumatic fever and the number of PMCs performed is low, this treatment should be restricted to expert operators in specialized centres to improve safety and procedural success rate.[661,664] Efforts should be made to increase the availability of PMC in lower-income countries, where access to treatment is limited for economic reasons.[665,666] Percutaneous mitral commissurotomy may be also considered in symptomatic patients with an MVA of >1.5 cm^2, if symptoms cannot be explained by another cause and if the anatomy is favourable (see *Table 8*). Percutaneous mitral commissurotomy should be considered as a first-line treatment for patients with anatomically suitable rheumatic MS and mild-to-moderate calcification without severe subvalvular impairment. Selected patients with unfavourable anatomical and clinical characteristics can still benefit from PMC, particularly if they are at increased surgical risk. When symptomatic restenosis occurs after surgical commissurotomy or PMC, reintervention in most cases requires surgical valve replacement, but redo PMC can be proposed in selected candidates with favourable characteristics, if the predominant mechanism is commissural refusion. Long-term follow-up has shown favourable results following PMC despite a growing number of elderly patients with suboptimal clinical and anatomical characteristics.[663–665]

For patients in whom PMC is contraindicated (*Table 8*), surgical MV repair or, more frequently, replacement are good alternatives. Although repair is much more challenging than for PMR, it can be attempted at experienced centres.[663]

For patients with multiple VHD including MS, a comprehensive evaluation by the Heart Team and an individualized approach is necessary. Surgery is preferable to PMC in patients with severe MS and severe AV disease, unless the surgical risk is high. In selected cases with severe MS and moderate AV disease, PMC can be performed to postpone surgical treatment of both valves.

In high-risk cases with concomitant severe TR, PMC may be considered in selected patients with sinus rhythm, moderate atrial enlargement, and secondary TR due to post-capillary PH. In non-high-risk cases, surgery on both valves is preferred.[651,652,662,667] Treatment of patients with low-gradient severe MS (MVA <1.5 cm^2, mean gradient <10 mmHg) is challenging, because these patients are often older and have unfavourable anatomy.[668,669]

10.2.4. Follow-up

Asymptomatic patients with clinically severe MS who have not undergone intervention should be followed up yearly by TTE, and at longer intervals (2–3 years) in cases of moderate stenosis. After PMC, the post-procedural MVA and mean mitral gradient are important parameters that influence long-term clinical outcomes. Follow-up of patients after successful PMC is necessary because asymptomatic restenosis may occur. Progressive rheumatic involvement of other valves should be periodically assessed, irrespective of the therapy modality. Finally, education and the engagement of the family is key in patients with rheumatic MS, since it usually affects young individuals and women of childbearing age.

10.3. Degenerative mitral stenosis with mitral annular calcification

Patients presenting with MAC are elderly and have significant comorbidities, including disease of other valves. Mitral annular calcification is also an indicator of cardiovascular disease severity and is associated with an increased risk of AF, stroke, and death.[670,671] The incidence of MAC varies substantially, depending on the age of the studied population and the imaging modality used. It can be a consequence of many different pathological processes and, depending on the underlying disease, can be accompanied by stenosis, regurgitation, or both. However, most patients with MAC do not have significant valvular dysfunction.[647,672]

Generally, MS occurs due to calcific extension into the MV leaflets or subvalvular apparatus, and in some patients it is associated with combined MR.[673] Treatment options (including transcatheter and surgical approaches) are high-risk procedures and evidence from RCTs is lacking.

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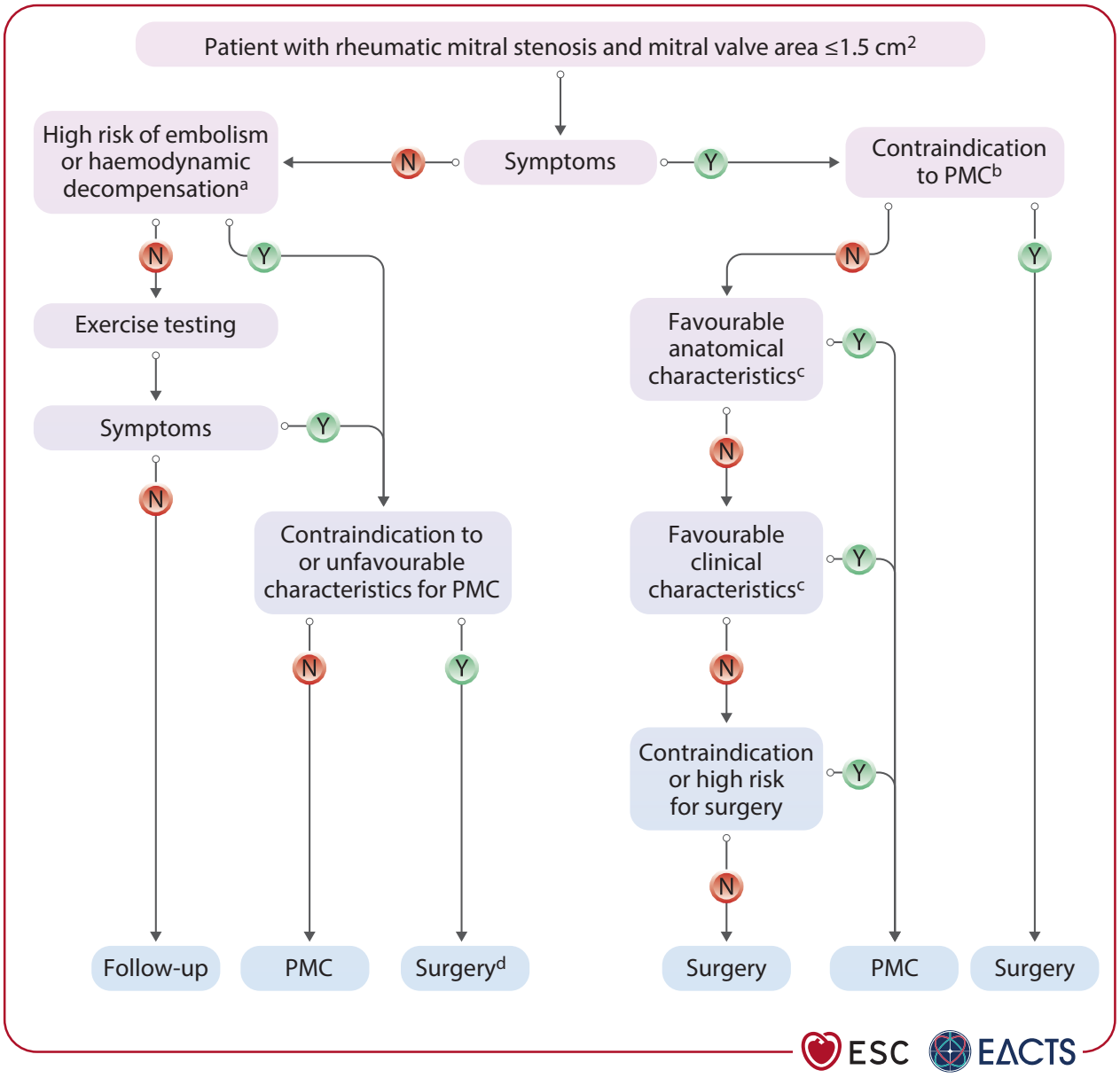

Figure 14 Management of clinically severe rheumatic mitral stenosis (mitral valve area ≤1.5 cm^2). AF, atrial fibrillation; LA, left atrium; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; NCS, non-cardiac surgery; NYHA, New York Heart Association; PH, pulmonary hypertension; PMC, percutaneous mitral commissurotomy; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation. [a]High thromboembolic risk: history of systemic embolism, dense spontaneous contrast in the LA, new-onset AF. High-risk of haemodynamic decompensation: SPAP >50 mmHg at rest, need for major NCS, desire for pregnancy or pregnant. [b]See *Table 8*. [c]Favourable = absence of unfavourable characteristics for PMC defined by unfavourable anatomical characteristics [echocardiographic score >8, Cormier score 3 (calcification of MV of any extent as assessed by fluoroscopy), severe TR] or unfavourable clinical characteristics (old age, history of commissurotomy, NYHA class IV, permanent AF, severe PH) (for the definition of scores see Supplementary data online, *Table S3*). [d]If operative risk is low.

10.3.1. Evaluation

Echocardiography is used for initial evaluation, but is frequently limited by acoustic shadowing due to severe calcification. Evaluation of MVA by planimetry is less reliable than in rheumatic MS, and TOE should therefore be used liberally. Degenerative MS can coexist with varying degrees of MR. Mean transmitral gradient has been shown to be associated with increased mortality irrespective of MR severity.[674] Electrocardiogram-gated CCT is necessary to assess the degree and locations of calcifications, especially if an intervention is planned.[647,674–676] Calcifications are usually more prominent at the posterior aspect of the annulus.

10.3.2. Indications for intervention

Intervention is recommended in symptomatic patients who are not responsive to medical therapy, weighing the potential benefits of the procedure against its associated risks. In elderly patients with degenerative MS and MAC, surgery is technically challenging and high risk. However,

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surgical MV repair or replacement with extensive decalcification and patch reconstruction of the annulus can be performed in selected patients at experienced centres (e.g. young patients post-chest radiation), where mortality rates of <5% have been reported.[677–679]

Degenerative MS is not amenable to PMC because commissural fusion is absent. In symptomatic high-risk patients with suitable anatomy, transcatheter implantation of a TAVI prosthesis in the mitral position is feasible but associated with frequent complications, including LVOT obstruction, valve embolization, stroke, and haemolysis due to PVL. Open surgical valve replacement via the LA with a TAVI device is an alternative that allows complete anterior leaflet removal;[680] however, mortality remains high. The use of dedicated TMVI devices is therefore encouraged because it appears to be safer.[542,681] Heart Team evaluation should guide the choice of treatment avoiding futility, because mortality remains high, even after successful treatment (10%–30% within 1 year).

Recommendation Table 8 — Recommendations on indications for percutaneous mitral commissurotomy, mitral valve surgery, and transcatheter intervention in clinically severe rheumatic and degenerative mitral stenosis (see also Supplementary data online, *Evidence Table 21*)

Recommendations	Class[a]	Level[b]
PMC is recommended in symptomatic patients in the absence of unfavourable characteristics for PMC.[c] [651–653,662,665]	I	B
PMC is recommended in any symptomatic patients with a contraindication or at high risk for surgery.	I	C
MV surgery is recommended in symptomatic patients who are not suitable for PMC.	I	C
PMC should be considered as initial treatment in symptomatic patients with suboptimal anatomy but no unfavourable clinical characteristics for PMC.[c]	IIa	C
PMC should be considered in asymptomatic patients without unfavourable clinical and anatomical characteristics for PMC, and: • High thromboembolic risk (history of systemic embolism, dense spontaneous contrast in the LA, new-onset or paroxysmal AF), and/or • High risk of haemodynamic decompensation (SPAP >50 mmHg at rest, need for major NCS, pregnant or desire for pregnancy).	IIa	C
TMVI may be considered in symptomatic patients with extensive MAC and severe MV dysfunction at experienced Heart Valve Centres with expertise in complex MV surgery and transcatheter interventions.[542,680,681]	IIb	C

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AF, atrial fibrillation; LA, left atrium/left atrial; MAC, mitral annular calcification; MV, mitral valve; NCS, non-cardiac surgery; NYHA, New York Heart Association; PH, pulmonary hypertension; PMC, percutaneous mitral commissurotomy; SPAP, systolic pulmonary artery pressure; TMVI, transcatheter mitral valve implantation; TR, tricuspid regurgitation.
[a]Class of recommendation.
[b]Level of evidence.
[c]Unfavourable characteristics for PMC can be defined by the presence of several of the following characteristics: clinical characteristics (old age, history of commissurotomy, NYHA class IV, permanent AF, severe PH); anatomical characteristics [echocardiographic score >8, Cormier score group 3 (calcification of MV of any extent as assessed by fluoroscopy), severe TR] (for the definition of scores see Supplementary data online, *Table S3*).

Table 8 Contraindications for percutaneous mitral commissurotomy in rheumatic mitral stenosis

Contraindications
MVA >1.5 cm^2 [a]
LA thrombus[b]
More than mild MR
Severe or bi-commissural calcification
Absence of commissural fusion
Severe concomitant AV disease, or severe combined tricuspid stenosis and regurgitation requiring surgery
Concomitant CAD requiring bypass surgery

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AV, aortic valve; CAD, coronary artery disease; LA, left atrium/left atrial; MR, mitral regurgitation; MVA, mitral valve area; OAC, oral anticoagulation; PMC, percutaneous mitral commissurotomy; TOE, transoesophageal echocardiography.
[a]PMC may be considered in patients with MVA of >1.5 cm^2 with symptoms that cannot be explained by another cause and if the anatomy is favourable.
[b]When the thrombus is located in the LA appendage, PMC may be considered in patients with contraindications to surgery or those without urgent need for intervention, in whom OAC can be safely given for 1–3 months, provided repeat TOE confirms resolution of thrombus.

11. Tricuspid regurgitation

11.1. Prevalence and aetiology

TR is a common echocardiographic finding in the general population, with higher prevalence in women and older patients. Trivial or mild TR is mostly a benign condition. Significant TR (≥ moderate) has a reported age- and sex-adjusted prevalence of 0.55% (4% in people aged ≥75 years).[682] Severe TR is associated with increased risk of death and HF, independent of comorbidities, ventricular function, and pulmonary pressures.[683–686]

Only 8%–10% of patients with TR present with clear anatomical abnormalities of the TV apparatus (primary TR), which can be due to infective endocarditis, RHD, carcinoid syndrome, congenital abnormalities (e.g. Ebstein's anomaly), chest radiation, or myxomatous disease, as well as trauma or iatrogenic valve damage (e.g. after endomyocardial biopsy).[682] Cardiac implantable electronic device (CIED)-related TR represents a separate entity requiring a specific diagnostic approach and management.[687] In patients with a CIED, diagnostic efforts should be made to clarify if the lead is the cause of TR (CIED-related TR) or incidental (CIED-associated TR).[688]

In patients with secondary TR, TV leaflets are structurally normal and regurgitation is caused by annular dilatation and/or leaflet tethering due to RA dilatation, and/or RV dilation and dysfunction. Based on the main morphological and haemodynamic characteristics, two phenotypes of secondary TR have been proposed:[689] (i) atrial secondary TR, mainly due to AF and characterized by the absence of significant leaflet tethering, but with marked RA and annular dilatation along with preserved RV size/function, pulmonary pressure, and LV function; and (ii) ventricular secondary TR, due to annular dilatation and leaflet tethering as a consequence of left-sided ventricular or valvular disease (post-capillary PH), pre-capillary PH, or primary RV cardiomyopathy/ischaemia (also after left-sided valve surgery).[690] At an advanced disease stage, these two phenotypes may no longer be distinguishable, and therefore early characterization is key to determine outcome.[691,692] Evidence of an impact on patient management is currently lacking; therefore, current recommendations for intervention consider mainly primary vs secondary TR.

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11.2. Evaluation

Echocardiography is recommended to assess patients with TR[45] and should include evaluation of severity and aetiology (including characterization of left-sided heart disease and, if applicable, CIED lead location and interaction with the valve apparatus), the impact of TR on the right-sided chambers (RV and RA size and function), and assessment of central venous (inferior vena cava) and pulmonary pressures. Transthoracic echocardiography provides sufficient diagnostic information in most patients. Transoesophageal echocardiography is necessary for when visualization of the TV apparatus. In candidates for an intervention, advanced techniques, such as strain analysis and 3D echocardiography, should also be applied when available.

Assessment of TR severity should be ideally performed in euvolaemic status, with optimized pulmonary and systemic pressures, and based on an integrative approach considering multiple qualitative and quantitative parameters (*Figure 15*).[45,693] A grading scheme extending beyond severe, including 'massive' and 'torrential' grades, has been proposed to refine TR reduction assessment after transcatheter interventions and has been used in several studies.[694,695] Although this five-grade scale may be associated with a proportional increase in symptoms and event risk,[694,695] an intervention should be considered without delay, as soon as TR is severe, with the aim of reducing TR to moderate or less.[696,697]

Echocardiographic assessment of the RV is challenging due to its complex geometry, imaging constraints, and the high dependency on loading conditions. When accurate measurements of RV size and function, as well as RV volume, are necessary for decision-making, CMR should be used because of its high accuracy and reproducibility.[698,699] In *Figure 15*, upper limits of normal for different RV size parameters are provided to guide definition of RV dilatation and remodelling. In the setting of severe TR, RV function is often overestimated and therefore the most conservative/cautious thresholds are suggested for the currently used echocardiographic parameters to identify RV dysfunction at the earliest stage possible. Cut-off values for severe RV dysfunction are also provided to indicate high-risk or possibly futile interventions. Although robust validation is lacking, all these reference values are chosen based on large multicentre reports of normative data and outcomes.[60,697,700–704]

Echocardiography often underestimates pulmonary pressures in cases of severe TR.[705] Right heart catheterization is therefore recommended in all candidates for an intervention to assess the haemodynamic consequences of TR on the RA and venous circulation (e.g. ventricularization of the RA pressure curves), measure end-diastolic RV pressure, and document volume overload. The assessment of pulmonary pressures and vascular resistance are key to exclude masked severe pre-capillary PH.[706]

RV–pulmonary artery coupling refers to the ability of the RV systolic performance to match a given pulmonary afterload maintaining adequate cardiac output, and can be measured invasively or approximated using echocardiography [i.e. tricuspid annular plane systolic excursion (TAPSE)/SPAP].[707,708] RV–pulmonary artery uncoupling (low TAPSE/SPAP) occurs when sustained increases in afterload cannot be matched by RV contractile reserve and has been associated with poor prognosis in different HF conditions, including severe TR. Although not yet prospectively validated, this index may improve risk stratification.

Electrocardiogram-gated CCT with dedicated protocols ensuring sufficient contrast enhancement of the right heart cavities provides detailed characterization of the RA, RV, and vena cava anatomy, the location of the right coronary artery, and is crucial to assess suitability and device sizing for several transcatheter interventions.[689,697]

Before any intervention is considered, careful evaluation of TR aetiology, disease stage (TR severity, RV and LV dysfunction, and PH), patient operative risk, and likelihood of recovery by a dedicated collaborative Heart Team is recommended (*Figure 16*). Dedicated clinical risk scores for TR patients have been described recently. The TRI-SCORE[709] and the STS isolated TV risk calculator[710] take into consideration clinical and echocardiographic signs of RV dysfunction, and secondary organ (particularly hepatic and renal) impairment. They both allow improved estimates of peri-procedural risk in patients with severe TR undergoing surgery and possibly help to avoid futile interventions.[84,711] The importance of risk stratification was demonstrated in a recent registry analysis ($n = 2413$) comparing any interventions with conservative management. Early TV intervention (transcatheter valve repair or surgery) was associated with improved mid-term survival in patients with a low or intermediate TRI-SCORE (up to 5 points), while patients with a high TRI-SCORE (≥6) did not derive any benefit compared with conservative management.[696] Moreover, isolated TV surgery (repair or replacement) improved survival at 10 years in patients with a low TRI-SCORE (≤3). The same benefit was observed in patients with an intermediate TRI-SCORE (4–5) after successful TV repair only.[689,697,709] Patients with moderate or severe TR should be regularly followed up clinically and by echocardiography at least every 6 months.

11.3. Medical therapy

Patients with relevant TR should be first treated according to the assumed aetiology, including optimal HF treatment, pulmonary vasodilators for PH, and rhythm control for AF.[339,693]

In the case of HF symptoms, diuretics should be initiated in a stepwise approach,[339] beginning with loop diuretics eventually combined with aldosterone antagonists, thiazide diuretics, and/or SGLT2is.[712] However, according to current knowledge, medical therapy has very limited effect on the evolution of TR severity and none of these measures should delay evaluation of an intervention at an expert centre.[713]

11.4. Indications for intervention

11.4.1. Surgery

Patients are often referred too late for surgery when significant RV and other organ failure have occurred. Isolated TV surgery has therefore been considered to be generally high risk, with in-hospital mortality rates of 8%–10% in several reports,[714,715] but contemporary cohorts have demonstrated improved outcomes when patients are referred earlier and more effective techniques are used.[716] Valve repair using an annuloplasty ring is preferred over replacement, whenever technically feasible, especially in low-risk patients with suitable anatomy.[709] However, TV replacement may be necessary in cases of advanced disease with marked annular dilatation and leaflet tethering.[688,717] For CIED-related TR, preparation of any entrapped tricuspid leaflet and possibly lead extraction with implantation of an epicardial system has been associated with improved TV function.[688,717]

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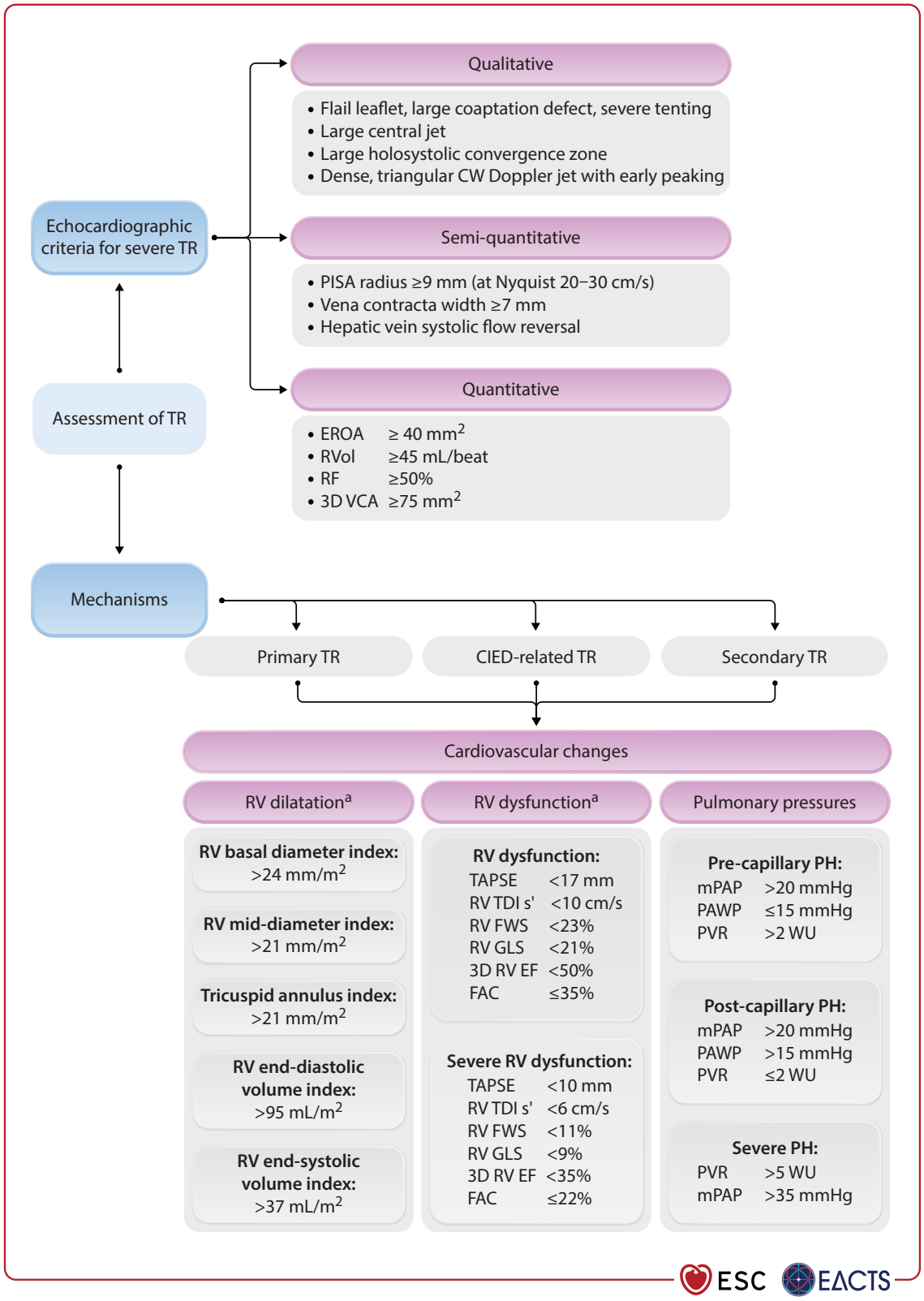

Figure 15 Echocardiographic and invasive assessment of tricuspid regurgitation. 3D, three-dimensional; CIED, cardiac implantable electronic device; CW, continuous-wave; EROA, effective regurgitant orifice area; FAC, fractional area change; FWS, free wall strain; GLS, global longitudinal strain; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PISA, proximal isovelocity surface area; PVR, pulmonary vascular resistance; RF, regurgitant fraction; RV, right ventricle/ventricular; RVEF, right ventricular ejection fraction; RVol, regurgitant volume; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; TR, tricuspid regurgitation; VCA, vena contracta area; WU, wood unit.
[a]RV apical focused view.

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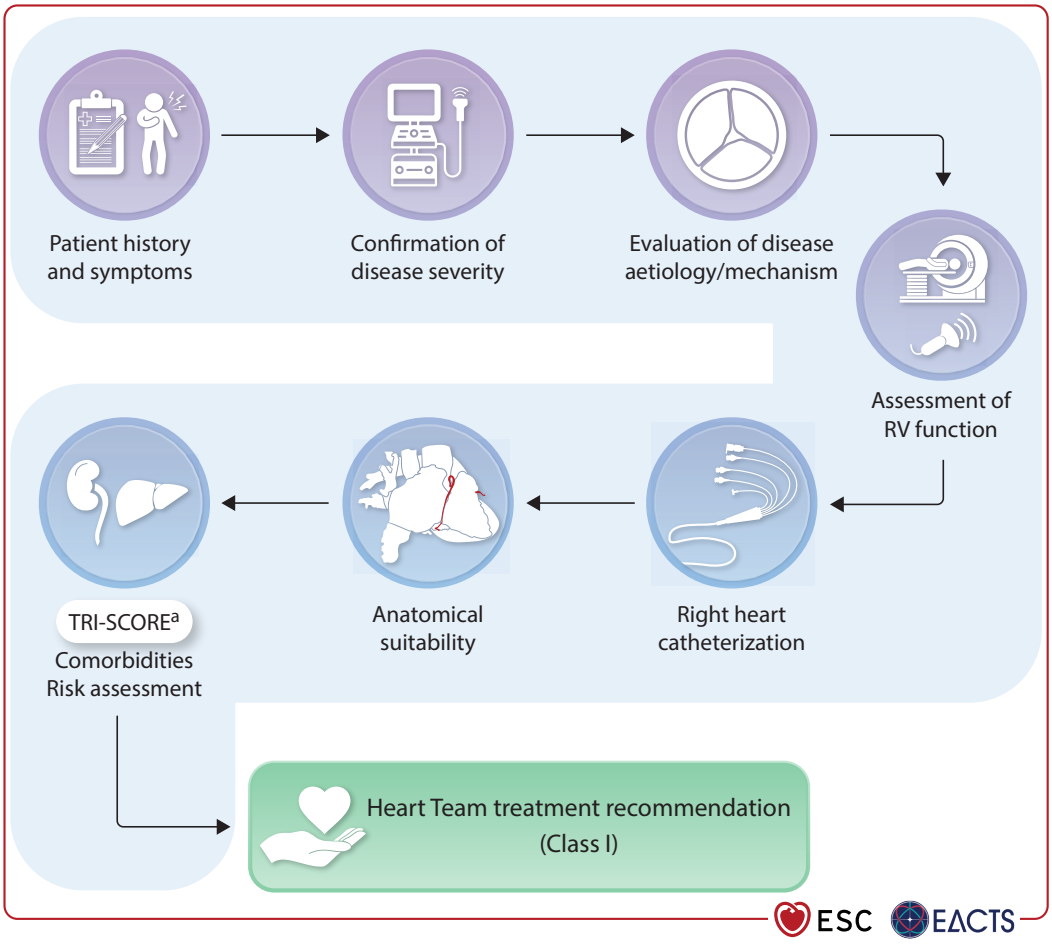

Figure 16 Stepwise evaluation of patients with tricuspid regurgitation. RV, right ventricle/right ventricular. [a]See Supplementary data online, *Table S4*.

11.4.1.1. Patients without indication for left-sided valve surgery

In patients with severe TR but without the need for left-sided valve surgery, surgical intervention is recommended in operable symptomatic patients with primary TR (*Figure 17*; *Recommendation Table 9*).[718] Furthermore, it should be considered in symptomatic patients with secondary TR, or in asymptomatic patients with primary or secondary TR and signs of RV dilatation or RV function deterioration.[719] However, patients with severe LV/RV dysfunction or PH do not qualify due to high operative risk.[84,686,720]

11.4.1.2. Patients with indication for left-sided valve surgery

Severe primary or secondary TR is unlikely to improve after isolated surgical treatment of left-sided valve disease, and reoperation for TR treatment is associated with high peri-operative mortality.[721] Therefore, TV surgery is recommended at the time of the index procedure.

Mild TR with associated significant annular dilatation or moderate TR, if left uncorrected at the time of left-sided valve surgery, will progress in approximately one-quarter of patients and is associated with worse outcome.[690,722] In patients with moderate TR, TV repair annuloplasty during MV surgery should be considered, because large retrospective studies[723,724] and two recent RCTs have shown beneficial effects on TR progression and RV remodelling over time.[725,726] However, no effects on mortality, HF events, or reoperation were observed in the repair group.[725,727] Concomitant TV repair has also been associated with a higher risk of conduction disturbances requiring pacemaker implantation (up to 14%),[725,728] with potential negative impacts on longer-term outcomes.[729,730] In patients with mild TR and annular dilatation (≥40 mm or >21 mm/m^2) undergoing left-sided valve surgery, previous observational studies have demonstrated a benefit of concomitant TV repair in terms of TR progression[723,724] and RV function,[731] and a trend towards improved long-term survival.[724] However, a subanalysis of a recent RCT did not identify any difference in the progression of TR or other outcomes in this category of patients

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during a 2-year follow-up period.[725] In turn, the need of pacemaker implantation after surgery led to a subsequent increase in HF hospitalizations, endocarditis, and mortality.[729] Annuloplasty may therefore be considered after careful evaluation of the risk factors for progressive annular dilatation and TR (AF, RA size, pulmonary pressures, etc.), balancing against the risk of possible pacemaker implantation (Supplementary data online, *Table S5*).[732]

11.4.2. Transcatheter techniques

Several transcatheter approaches for the treatment of TR have been developed, including TEER, direct annuloplasty, and orthotopic and heterotopic TV replacement. Data from large multicentre registries, single-arm clinical trials, and two recent RCTs in patients with severe TR at intermediate and high risk for surgery have shown the safety of transcatheter repair, as well as the ability to reduce TR to moderate or less in

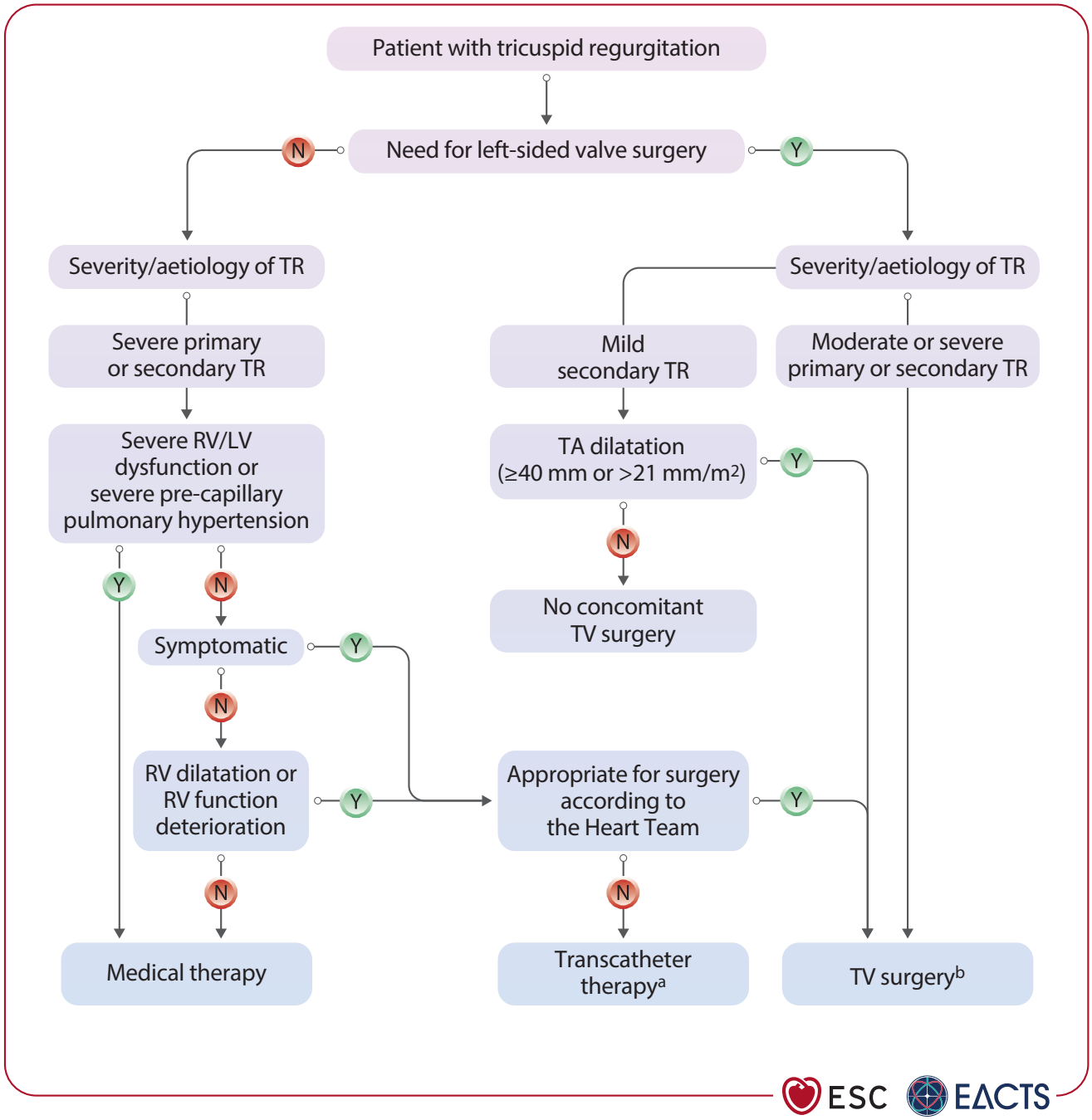

Figure 17 Management of patients with tricuspid regurgitation. LV, left ventricle/left ventricular; RV, right ventricle/right ventricular; TA, tricuspid annulus; TR, tricuspid regurgitation; TV, tricuspid valve. [a]The Heart Team with expertise in the treatment of TV disease evaluates anatomical eligibility for transcatheter therapy including jet location, coaptation gap, leaflet tethering, and potential interference with pacing lead. [b]Repair whenever possible, particularly in cases of moderate TR or mild TR with significant TA dilatation.

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more than 80% of cases when anatomical suitability was confirmed.[713,733–735] The Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System (TRILUMINATE) Pivotal Trial showed also a lower incidence of the composite endpoint of death from any cause or TV surgery, HF hospitalization, and improvement in quality of life as measured with the KCCQ score after tricuspid TEER compared with medical treatment that was exclusively driven by improved quality of life [11.7 points (95% CI, 6.8–16.6); P <0.001].[713] At 2 years, a lower incidence of HF hospitalizations has been observed in the intervention group, despite a high rate of crossovers (59%).[736]

Another investigator-initiated RCT (the Tri.Fr trial) demonstrated the benefit of tricuspid TEER in combination with GDMT over medical therapy alone, for a composite score driven by improved PROMs.[737] Another recent RCT (the Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy using a Novel Device (TRISCEND) II trial), comparing transcatheter TV replacement with optimized medical therapy in patients with symptomatic severe TR, showed similar results with a win ratio favouring TV replacement mainly explained by symptom and quality-of-life improvement. In these studies, reverse RV remodelling was also observed. However, the safety profile of transcatheter TV replacement was less favourable, including higher risk for major bleeding (15%) and post-procedural pacemaker implantation in about one-quarter of the pacemaker-naïve patients after 12 months of follow-up.[738] Based on these data, transcatheter treatment should be considered to improve quality of life and RV remodelling in high-risk patients with symptomatic severe TR, despite optimal medical therapy, but without severe RV dysfunction or pre-capillary PH.

Transvenous CIED lead repositioning or extraction can be considered in selected patients to improve TR or avoid lead jailing before any tricuspid interventions, although the efficacy of this procedure is uncertain and the risk of damaging the TV not negligible.[688,717,739]

Recurrent TR after previous tricuspid annuloplasty usually requires cardiac reoperation for surgical TV replacement. Transcatheter valve-in-ring implantation is an off-label procedure to treat residual TR in high-risk patients. Challenges are the non-circular shape and the open form of the surgical annuloplasty ring.[740] However, transcatheter tricuspid valve-in-valve procedures have been performed with satisfactory results.[741]

Transcatheter TV procedures should be performed at an experienced Heart Valve Centre with expertise in the treatment of TV disease (*Table 6*). Careful evaluation of clinical and anatomical suitability is key for appropriate patient and device selection to achieve optimal TR reduction and symptomatic response to the therapy.

Recommendation Table 9 — Recommendations on indications for intervention in tricuspid regurgitation (see also Supplementary data online, *Evidence Tables 22 and 23*)

Recommendations	Class[a]	Level[b]
Careful evaluation of TR aetiology, stage of the disease (i.e. degree of TR severity, RV and LV dysfunction, and PH), patient operative risk, and likelihood of recovery by a multidisciplinary Heart Team is recommended in patients with severe TR prior to intervention.[691,742]	I	C
Patients with tricuspid regurgitation and left-sided valvular heart disease requiring surgery		
Concomitant TV surgery[c] is recommended in patients with severe primary or secondary TR.[725,731,743,744]	I	B
Concomitant TV repair should be considered in patients with moderate primary or secondary TR, to avoid progression of TR and RV remodelling.[723,724,726,731]	IIa	B
Concomitant TV repair may be considered in selected patients with mild secondary TR and tricuspid annulus dilatation (≥40 mm or >21 mm/m^2), to avoid progression of TR and RV remodelling.[723–726,731,743]	IIb	B
Patients with severe tricuspid regurgitation without left-sided valvular heart disease requiring surgery		
TV surgery[c] is recommended in symptomatic patients with severe primary TR without severe RV dysfunction or severe PH.	I	C
TV surgery[c] should be considered in asymptomatic patients with severe primary TR who have RV dilatation/RV function deterioration, but without severe LV/RV dysfunction or severe PH.	IIa	C
TV surgery[c] should be considered in patients with severe secondary TR who are symptomatic or have RV dilatation/RV function deterioration, but without severe LV/RV dysfunction or PH.[685,720,745–747]	IIa	B
Transcatheter TV treatment should be considered to improve quality of life and RV remodelling in high-risk patients with symptomatic severe TR despite optimal medical therapy in the absence of severe RV dysfunction or pre-capillary PH.[713,733,735,738,748–751]	IIa	A

LV, left ventricle/left ventricular; PH, pulmonary hypertension; RV, right ventricle/right ventricular; TR, tricuspid regurgitation; TV, tricuspid valve.
[a]Class of recommendation.
[b]Level of evidence.
[c]Valve repair whenever possible.

12. Tricuspid stenosis

12.1. Prevalence and aetiology

Tricuspid stenosis (TS) is a relatively rare disease that is most commonly associated with congenital conditions or enzymatic disorders, such as Whipple's or Fabry's disease. It can also be acquired as an isolated manifestation of RHD or occur in combination with aortic and/or MV involvement. Moreover, TS can be the consequence of carcinoid disease due to serotonin-mediated proliferation, causing apposition of fibroblasts and extracellular matrix on the valve leaflets and the subvalvular apparatus. Rare causes include medications (e.g. fenfluramine or methysergide) or inflow obstruction due to CIED-associated thrombus formation or endocarditis with large vegetations.

12.2. Evaluation

Valve evaluation and diagnosis of TS is based on echocardiography, and consists of the anatomical assessment of the leaflet tissue and the subvalvular apparatus. Leaflet thickening with or without calcifications and

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commissural fusions are pathognomonic findings of rheumatic involvement. A mean diastolic transvalvular gradient of >5 mmHg at a normal heart rate indicates severe TS.[649]

12.3. Medical therapy

Medical therapy is a bridge to surgical or transcatheter intervention. Intensive sodium restriction and concomitant diuretic therapy can lead to symptom improvement and diminish hepatic congestion.

12.4. Indications for intervention

Although valve repair is preferred in younger patients,[752] valve replacement is frequently required (see *Recommendation Table 10*). Biological heart valves have demonstrated adequate mid- and long-term results, and are preferred over MHVs because of high thrombogenicity in the low-pressure system.[753] In the case of BHV degeneration, transcatheter valve-in-valve procedures are good alternatives to re-replacement.[754] Transcatheter TV implantation is an emerging field, although limited experience is available for the treatment of TS.[749,755] In patients with carcinoid disease, a stable oncological situation is a prerequisite for any valve intervention to maximize survival and valve durability.[756]

Although data are very limited, TV balloon valvuloplasty can be an option in selected patients with TS (and no relevant TR), as well as in those with concomitant mitral and tricuspid rheumatic pathology.[757] However, in contrast to rheumatic MS, tricuspid rheumatic disease more frequently presents as combined stenosis and regurgitation, which limits the applicability of balloon valvuloplasty.

Recommendation Table 10 — Recommendations on indications for intervention in tricuspid stenosis

Recommendations	Class[a]	Level[b]
Surgery[c] is recommended in symptomatic patients with severe TS.[d]	I	C
Surgery[c] is recommended in patients with severe TS undergoing left-sided valve intervention.[e]	I	C

MV, mitral valve; PMC, percutaneous mitral commissurotomy; TS, tricuspid stenosis; TV, tricuspid valve.
[a]Class of recommendation.
[b]Level of evidence.
[c]Usually TV replacement.
[d]Percutaneous balloon valvuloplasty can be attempted as a first approach if TS is isolated.
[e]Percutaneous balloon valvuloplasty can be attempted if PMC can be performed on the MV.

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13. Multiple and mixed valvular heart disease

13.1. Prevalence and undertreatment

Patients frequently present with disease of more than one native heart valve [multiple VHD (MVHD)], or coexisting stenosis and regurgitation of the same valve (mixed VHD).[758] While the main cause of MVHD or mixed VHD has shifted to degeneration in high-income countries, the leading aetiology in low- and middle-income countries remains RHD.[758,759] Regurgitation of atrioventricular valves secondary to cardiomyopathy or long-standing primary valve disease, and late effects of radiation therapy, are further causes of MVHD.[758,760] Challenges in diagnostic evaluation coupled with limited data to guide clinical decisions contribute to late referral and undertreatment of patients with MVHD.[758]

13.2. Evaluation and diagnostic pitfalls

In view of the complex haemodynamic interplay of multiple and mixed valve lesions, assessment by a Heart Team at a Heart Valve Centre and use of an integrative multimodality approach is key to gain diagnostic certainty, detect cardiac damage, and evaluate therapeutic options.[761,762] In the light of paucity of data on diagnostic and prognostic parameters in patients with MVHD, assessment largely focuses on pathophysiological considerations and evidence derived from isolated valve lesions.

Echocardiography is the main tool to diagnose MVHD, assess mechanism, severity, and associated cardiac damage, and monitor disease progression.[761] Haemodynamic interdependence between multiple valve defects alters the loading and flow conditions, thereby limiting the diagnostic validity of measures established to grade single valve defects (*Table 9*). In the presence of MVHD, low-flow states are frequent. The continuity equation becomes erroneous if transvalvular flows are unequal, and pressure half-time (PHT)-derived methods are inaccurate if the ventricular compliance or filling is altered.[761] In this context, TOE can provide important detailed anatomical and mechanistic flow-independent information.[46,761]

If symptoms or echocardiographic findings are equivocal, multimodality diagnostics should be considered on an individual basis to assess the cumulative repercussions of MVHD.

Measures obtained during cardiopulmonary exercise testing reflect the effect of MVHD on functional capacity.[52,105,654,761,779] Levels of natriuretic peptides such as NT-proBNP correlate with functional and echocardiographic parameters, and provide incremental prognostic value in patients with mixed aortic disease and MVHD.[98,780] AV calcium scoring confirms the diagnosis of true severe AS under low-flow conditions, as described in *Section 8.2*.[777] Cardiac magnetic resonance imaging enables the independent assessment of valvular regurgitation using volumetric methods or direct flow quantification.[45,46,522,762,781] Importantly, invasive cardiac output-derived measures based on thermodilution or the Fick equation using estimated oxygen uptake are inaccurate in low-flow conditions or severe TR, commonly present in MVHD.[782]

13.3. Indications for intervention

Given the heterogeneity of clinical scenarios and the lack of evidence on optimal treatment pathways, it is recommended that patients with MVHD are evaluated for intervention by a collaborative Heart Team at a Heart Valve Centre with experience in multimodality imaging and treatment of complex VHD.[16,764]

Patients presenting with a lesion fulfilling criteria for an intervention based on recommendations for single VHD should be treated accordingly. In the remaining patients, assessment of symptoms and functional status, as well as cardiac damage (which may be masked by the consequences of concomitant lesions and occur before symptoms manifest), is required. The risk–benefit ratio of intervention needs to take into account diagnostic (un)certainty, the mechanisms and severity of MVHD, and patient-specific factors, as well as procedural options and risks to determine the mode, timing, and sequence of valve treatment.

13.3.1. Multiple valvular heart disease

Multiple VHD with primary (as opposed to secondary) valvular disease usually requires surgical treatment of all relevant valvular lesions. Simultaneous treatment of concomitant severe valve defects is recommended and treatment of concomitant moderate AS, or moderate TR, should be considered (*Recommendation Table 11*).

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Table 9 Echocardiographic pitfalls, robust measures, and complementary multimodality imaging parameters in multiple or mixed valvular heart disease

		Valve lesion to be assessed			
		AS	**AR**	**MS**	**MR**
Concomitant valve lesion	**AS**	—	PHT unreliable LV volume increase less pronounced *(hypertrophy, disproportionate diastolic LV pressure overload[763])*	PHT unreliable *(LV compliance ↓ [764])* Low gradient due to low flow possible *(low-flow state[669])*	Regurgitant volume ↑ MR colour-flow jet area ↑ *(increased afterload and transmitral systolic pressure gradient[46])*
	AR	Simplified Bernoulli equation overestimates gradient if LVOT velocity ↑ [765]	—	PHT unreliable *(gradient ↓, altered LV compliance[766])* MVA by continuity equation using aortic forward flow unreliable[46]	Doppler volumetric method using net aortic forward flow invalid Mitral-to-aortic VTI ratio unreliable *(increased transaortic flow[46])*
	MS	Low-flow low-gradient possible *(low-flow state[761])*	LV volume increase less pronounced *(reduced preload[761])*	—	Mitral-to-aortic VTI ratio unreliable *(increased mitral VTI due to stenosis[767])* Calcifications may shadow jet area
	MR	Low-flow low-gradient *(MR-induced low-flow state[768])* AS confused with MR jet	PHT unreliable *(altered LV compliance[763])* Doppler volumetric method using net mitral forward flow invalid *(increased flow[46])*	PHT unreliable *(altered LA and LV compliance[769,770])* Continuity equation unreliable *(increased transmitral flow[761])*	—
	TR	Low-flow low-gradient possible *(TR induced low-flow state[771])*	—	Low gradient possible *(low-flow state[668])* PHT may be less reliable *(impaired LV filling due to ventricular interdependence[772,773])*	Regurgitant volume↓ in SMR possible *(decreased preload[774])*
Robust echocardiography measurements		AVA (continuity equation), DVI[761] *In mixed AR and AS: V_{max} and mean gradient reflect combined burden[765]*	EROA (PISA), vena contracta[46,761]	Planimetry and 3D MVA (TOE)[529,775] *In mixed MR & MS: mean gradient reflects combined burden[674,776]*	EROA (PISA), vena contracta[46,761]
Alternative imaging modalities		CT: AV calcium scoring[777]	CMR: regurgitant volume and fraction[45,46]	—	CMR: regurgitant volume and fraction[45,46]

Measures reported refer to assessment of the valve lesions listed in the columns. Adapted from [761].
3D, three-dimensional; AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; CMR, cardiac magnetic resonance; CT, computed tomography; DVI, Doppler velocity index; EROA, effective regurgitant orifice area; LA, left atrium/left atrial; LV, left ventricle/left ventricular; LVOT, left ventricular outflow tract; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; PHT, pressure half-time; PISA, proximal isovelocity surface area; SMR, secondary mitral regurgitation; TOE, transoesophageal echocardiography; TR, tricuspid regurgitation; VHD, valvular heart disease; V_{max}, peak transvalvular velocity; VTI, velocity time integral; ↑, increase; ↓, decrease; —, none.

Transcatheter treatment options are established for severe AS (TAVI), rheumatic MS (PMC), and primary MR and TR (TEER or transcatheter replacement) in patients with MVHD at high surgical risk, if anatomy is suitable.[401,783] In the context of a transcatheter strategy, a staged approach—typically beginning with the downstream lesion (aortic, followed by mitral and tricuspid)—is generally preferred to avoid potential haemodynamic deterioration.[784,785]

MVHD with severe secondary regurgitation of both atrioventricular valves is usually the consequence of either HFrEF with ventricular SMR and secondary TR, or atrial dilatation leading to both atrial MR and TR

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(often TR > MR). While surgery aims to address all relevant valve lesions in a single procedure, a stepwise transcatheter strategy offers the possibility of reassessing the upstream valve(s) under altered loading conditions, usually 3 months after the initial intervention. In very selected cases simultaneous transcatheter valve treatment may be considered.[788,789] However, evidence is limited and primarily derived from modestly sized observational studies.[786–789]

13.3.2. Mixed aortic valve disease

The severity of mixed AV disease is often underestimated and patients with balanced moderate AR and AS show adverse event rates comparable to patients with severe isolated AS.[790,791]

Transvalvular gradients measured by Doppler reflect the overall haemodynamic burden of both regurgitation and stenosis, and are strongly associated with adverse outcomes.[765,791–793] Therefore, the presence of high transvalvular gradients justifies valve intervention in patients with moderate mixed AV disease, even if regurgitation is graded as moderate and the calculated or planimetric AVA is >1 cm^2 (*Recommendation Table 12*). Patients presenting with mixed AV disease, but with gradients below thresholds for intervention, should undergo careful multimodality diagnostics including assessment of cardiac damage to inform individual treatment strategies. Global longitudinal strain and natriuretic peptides have shown incremental prognostic value beyond symptom status and single lesion severity in patients with preserved LVEF.[762,794–796]

13.3.3. Mixed mitral valve disease

Mixed MV disease is usually present in patients with rheumatic valve disease or MAC. If MVA is ≤1.5 cm^2, recommendations for isolated MS apply. However, patients with an MVA of >1.5 cm^2 and moderate MR may be evaluated for valve replacement based on symptoms, anatomical characteristics, transmitral gradient, and signs of cardiac damage such as LA dilatation, AF, or PH.[529,674,776,797]

Recommendation Table 11 — Recommendations on indications for surgery of concomitant left-sided valvular heart disease[a]

Recommendations	Class[b]	Level[c]
Concomitant aortic stenosis		
SAVR is recommended in patients with severe AS undergoing surgery for another valve.	I	C
SAVR should be considered in patients with moderate AS[d] undergoing surgery for another valve.	IIa	C
Concomitant aortic regurgitation		
AV surgery is recommended in patients with severe AR undergoing surgery for another valve.	I	C
Concomitant mitral regurgitation		
MV surgery is recommended in patients with severe MR undergoing surgery for another valve.	I	C

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AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; MR, mitral regurgitation; MV, mitral valve; SAVR, surgical aortic valve replacement; TV, tricuspid valve.
[a]Recommendations for surgery of concomitant TV disease are listed in *Section 11* and *Section 12*.
[b]Class of recommendation.
[c]Level of evidence.
[d]Defined as an AVA of 1.0–1.5 cm^2 (or mean aortic gradient of 25–40 mmHg) in normal-flow conditions. Clinical assessment is essential to determine whether SAVR is appropriate for an individual patient.

Recommendation Table 12 — Recommendations on indications for intervention in patients with mixed moderate aortic stenosis and moderate aortic regurgitation (see also Supplementary data online, *Evidence Table 24*)

Recommendations	Class[a]	Level[b]
Intervention is recommended in symptomatic patients with mixed moderate AV stenosis[c] and moderate regurgitation, and a mean gradient ≥40 mmHg or V_{max} ≥4.0 m/s.[790–793]	I	B
Intervention is recommended in asymptomatic patients with mixed moderate AV stenosis[c] and moderate regurgitation with V_{max} ≥4.0 m/s, and LVEF <50% not attributable to other cardiac disease.[791]	I	C

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AV, aortic valve; AVA, aortic valve area; LVEF, left ventricular ejection fraction; V_{max}, peak transvalvular velocity.
[a]Class of recommendation.
[b]Level of evidence.
[c]AVA >1 cm^2.

13.4. Follow-up

Due to the cumulative haemodynamic impact of MVHD or mixed VHD, progression of its severity and the development of cardiac damage may be faster than in single VHD.[761] Therefore, follow-up intervals should be adjusted according to individual patient characteristics.

14. Management of patients with prosthetic valves or valve repair

14.1. Choice of prosthetic valve

When choosing between an MHV and a BHV prosthesis for an individual patient, age, life expectancy, lifestyle, bleeding and thromboembolic risks, possibility of pregnancy, and patient preference should be considered. Life expectancy is estimated according to age, sex, comorbidities, ethnicity, and geographical area.[798] An MHV is preferred in younger patients with longer life expectancy and in those with a pre-existing indication for long-term OAC (*Recommendation Table 13*). Generally, a BHV is implanted in patients with shorter life expectancy, increased bleeding risk due to frailty or comorbidities, in women contemplating pregnancy, and in patients in whom stable INRs with adequate times in therapeutic range are unlikely.[799] Importantly, the performance of different BHV prostheses can vary considerably.[800] The impact of the aetiology of the native valve disease, if any, on the choice between an MHV and a BHV remains unexplored.

Several large observational studies, smaller RCTs, and meta-analyses have compared long-term mortality with BHV and MHV prostheses in patients aged 50–70 years.[376,801–805] Some of the studies showed lower mortality with an MHV in AV patients <60 years and MV patients <65 years old,[801,804] while others failed to show any differences.[376,802,803] Most of these studies were limited by their observational nature and missing information on the type of prostheses implanted. RCTs with sufficient statistical power comparing biological and mechanical prostheses are warranted.

Replacement of the AV using an autograft (Ross procedure) is an alternative to an MHV in young patients that should be performed at experienced centres by operators with dedicated expertise (see also *Section 8*).[806] General recommendations are summarized in *Recommendation Table 13*.

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Recommendation Table 13 — Recommendations for prosthetic valve selection

Recommendations	Class[a]	Level[b]
Mechanical heart valve		
An MHV is recommended according to the desire of the informed patient and if there is no contraindication to long-term anticoagulation.	I	C
An MHV should be considered in patients with an estimated long life expectancy,[c] if there are no contraindications for long-term OAC.[801,807–811]	IIa	B
An MHV should be considered in patients aged <60 years for prostheses in the aortic position and aged <65 years for prostheses in the mitral position.[801,807–811]	IIa	C
An MHV should be considered in patients with a pre-existing MHV in another position.	IIa	C
An MHV may be considered in patients with a clear indication for long-term OAC.	IIb	C
Biological heart valve		
A BHV is recommended according to the desire of the informed patient.	I	C
A BHV is recommended when an adequate quality of anticoagulation with VKA is unlikely, in patients at high bleeding risk, or with estimated short life expectancy.[c]	I	C
A BHV should be considered in patients aged >65 years for prostheses in the aortic position or aged >70 years for prostheses in the mitral position.	IIa	C
A BHV should be considered in women contemplating pregnancy.	IIa	C

BHV, biological heart valve; MHV, mechanical heart valve; OAC, oral anticoagulation; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Life expectancy should be estimated according to age, sex, comorbidities, ethnicity, and geographical area.

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14.2. Follow-up of patients with prosthetic valves

All patients with prosthetic valves require lifelong clinical and echocardiographic follow-up to detect deterioration of prosthetic function, associated cardiac damage, or progressive disease of another valve. Serial TTE measurements of transprosthetic gradients, calculation of the effective valve area, and evaluation of leaflet motion and morphology should be performed in patients receiving a BHV within 3 months after valve implantation, again at 1 year, and annually thereafter, or sooner if new cardiovascular symptoms occur.[812] TOE is recommended in all cases of suspected prosthetic valve dysfunction or endocarditis. In the latter case, CCT and PET-CT are also recommended, if the diagnosis is unclear, and to identify primary or secondary infection foci.[5]

Cinefluoroscopy for MHVs and CCT provide useful additional information, if valve thrombus or pannus is suspected.[812] Imaging should be repeated in the case of thrombolytic and antithrombotic treatment of MVH thrombosis, even if gradients are normalized.[813]

14.3. Antithrombotic therapy in patients with treated valvular heart disease

14.3.1. Mechanical heart valves

14.3.1.1. Post-operative anticoagulation and therapeutic targets

Mechanical heart valves require lifelong treatment with a VKA guided by the INR. Bridging with either therapeutic unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) and VKA should be initiated within 24 h after MHV implantation, or as soon as considered safe. Heparin can be stopped when the INR is documented for 2 consecutive days within the therapeutic range (*Figure 18*).[814] Two meta-analyses and a prospective study have suggested slightly lower bleeding rates using UFH bridging compared with LMWH after MHV replacement or cardiac surgery.[814–816] However, RCTs comparing the timing and dosage of each bridging strategy are lacking.

For all patients with an MHV, lifelong VKA is recommended to avoid major thrombotic complications, since cardioembolic or valve thrombosis rates without anticoagulation are substantial (12% per year and 22% per year for first-generation aortic and mitral MHVs, respectively).[817] The INR target and range should be chosen considering the type, position, and number of valves, the patient's thrombotic risk, and comorbidities (see *Table 10* and *Recommendation Table 14*). In patients with an MHV developing a major thromboembolic complication despite adequate INR and time in therapeutic range (TTR, usually defined as >60%),[820] either increased VKA intensity (e.g. INR target and range increased by 0.5 units) or the addition of low-dose acetylsalicylic acid (ASA) (75–100 mg/day) should be considered.[818] Direct oral anticoagulants or dual antiplatelet therapy (DAPT) are contraindicated to prevent thromboembolism in patients with an MHV.[821–824]

Given the complexity of lifelong VKA therapy due to high intra- and interpatient variability, the need for monitoring, drug and food interactions,[825,826] the narrow therapeutic window, influence of comorbidities, and non-modifiable characteristics (e.g. ageing, genetics, and ethnicity), RCTs have shown that patient's education, as well as disease and treatment awareness, significantly improves anticoagulation quality and adherence.[827–830] International normalized ratio self-monitoring and/or self-management increase efficacy, but not safety, as compared with a standard approach; INR self-monitoring can be used by motivated patients after adequate training.[827–830]

The indication for VKA and DAPT combination in MHV patients presenting with acute coronary syndrome is described in the corresponding ESC Guidelines.[151,831] In patients with an MHV and an indication for single antiplatelet therapy (SAPT) due to symptomatic major atherosclerotic diseases and low bleeding risk, low-dose ASA in combination with a VKA should be considered, because this strategy has been shown to significantly lower the incidence of major adverse cardiovascular events.[818] However, the combination of antiplatelet agents (single or dual) and VKA increases the risk of bleeding,[825] and therefore their use should be carefully weighted. In a large meta-analysis that included MHV patients, the combination of VKA with either ASA or clopidogrel increased clinically relevant bleeding compared with VKA alone (clopidogrel odds ratio, 3.55; 95% CI, 2.78–4.54; ASA odds ratio, 1.50; 95% CI, 1.29–1.74), which may be aggravated because of potential pharmacokinetic drug interactions on the cytochrome P (CYP)450s 2C19 and 3A4.[825]

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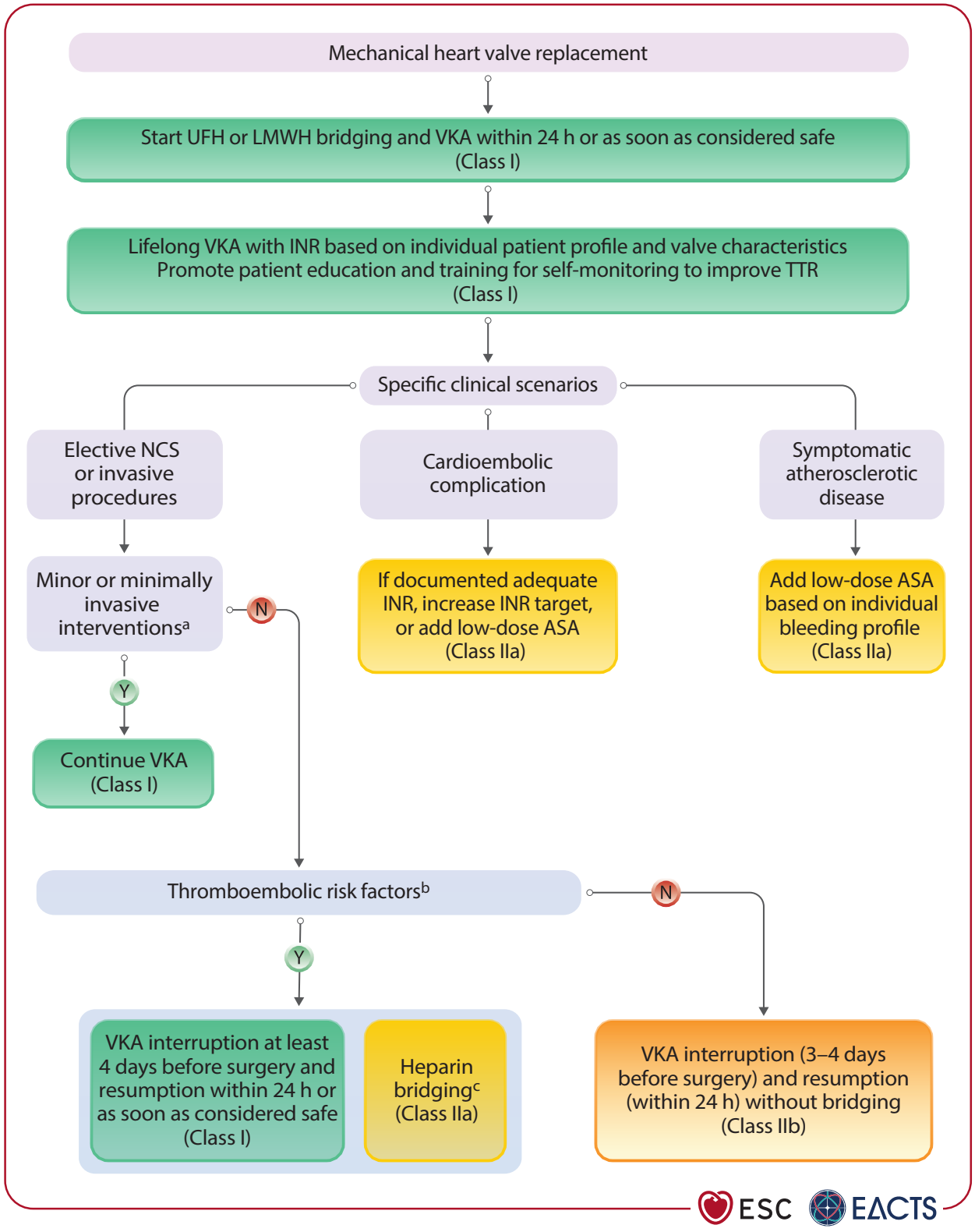
Mechanical heart valve replacement
Start UFH or LMWH bridging and VKA within 24 h or as soon as considered safe (Class I)
Lifelong VKA with INR based on individual patient profile and valve characteristics Promote patient education and training for self-monitoring to improve TTR (Class I)
Specific clinical scenarios
Elective NCS or invasive procedures
Cardioembolic complication
Symptomatic atherosclerotic disease
Minor or minimally invasive interventions[a]
N
Y
Continue VKA (Class I)
If documented adequate INR, increase INR target, or add low-dose ASA (Class IIa)
Add low-dose ASA based on individual bleeding profile (Class IIa)
Thromboembolic risk factors[b]
N
Y
VKA interruption at least 4 days before surgery and resumption within 24 h or as soon as considered safe (Class I)
Heparin bridging[c] (Class IIa)
VKA interruption (3–4 days before surgery) and resumption (within 24 h) without bridging (Class IIb)
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Figure 18 Antithrombotic therapy following mechanical heart valve implantation. AF, atrial fibrillation; ASA, acetylsalicylic acid; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; MS, mitral stenosis; N, no; NCS, non-cardiac surgery; TTR, time in therapeutic range; UFH: unfractionated heparin; VKA, vitamin K antagonist; Y, yes. [a]Skin; minor eye surgery including cataract; dental cleaning, treatment of caries, and dental extractions; pacemaker or device implantation; and diagnostic cardiac catheterization. [b]MHV in mitral or tricuspid position, older MHV generations in any position, inherited or acquired hypercoagulable state, LV dysfunction (LVEF <35%), AF with significant MS, recent (<12 months) major thrombotic event (i.e. cardioembolic stroke, deep vein thrombosis, pulmonary embolism). [c]Bridging needs to be started as soon as INR reaches a sub-therapeutic value and on the first postoperative day or as soon as considered safe.

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Recommendation Table 14 — Recommendations for the management of antithrombotic therapy in patients with a mechanical heart valve

Recommendations	Class[a]	Level[b]
Following cardiac surgery with MHV implantation, it is recommended to start UFH or LMWH bridging and VKA within 24 h, or as soon as considered safe.[815,816,832–834]	I	B
Lifelong OAC with a VKA is recommended for all patients with MHVs to prevent thromboembolic complications.[821–823,835–838]	I	A
INR self-monitoring and self-management are recommended over standard monitoring in selected, trained patients to improve efficacy.[827,828]	I	A
It is recommended that INR targets are based on the type and position of the MHV, patient risk factors, and comorbidities.[c] [818,819,835–838]	I	A
Patient education is recommended to improve the quality of OAC.[827–830]	I	A
The addition of low-dose ASA (75–100 mg/day) to VKA should be considered in selected patients with MHVs in case of concomitant symptomatic atherosclerotic disease considering the individual bleeding risk profile.[818]	IIa	B
Either an increase in INR target or the addition of low-dose ASA (75–100 mg/day) should be considered in patients with MHVs who develop a major thromboembolic complication despite documented adequate INR.[818]	IIa	C
DOACs and/or DAPT are not recommended to prevent thrombosis in patients with an MHV.[821–824]	III	A

ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; h, hour; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MHV, mechanical heart valve; OAC, oral anticoagulation; UFH, unfractionated heparin; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Table 10* for details.

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Table 10 International normalized ratio targets and therapeutic ranges for patients with a mechanical heart valve

MHV type and position	Additional pro-thrombotic factors[a]	INR target and (range)
First-line treatment with VKA only		
Ball-in cage, tilting disc valve in any position, all MHV in mitral/tricuspid position	No	3 (2.5–3.5)
	Yes	3.5 (3–4)[b]
Bileaflet, current-generation single-tilting aortic MHV	No	2.5 (2–3)[c]
	Yes	3 (2.5–3.5)

AF, atrial fibrillation; ASA, acetylsalicylic acid; INR, international normalized ratio; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; MS, mitral stenosis; VKA, vitamin K antagonist.
[a]Inherited or acquired hypercoagulable state, LV dysfunction (LVEF <35%), AF with significant MS, recent (<12 months) major thrombotic event (i.e. cardioembolic stroke, deep vein thrombosis, pulmonary embolism).
[b]In patients at very high thrombotic risk, low-dose ASA may be added instead.[818]
[c]In patients at high bleeding risk, INR target could be maintained at a lower interval: 2 (1.5–2.5).[819]

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14.3.1.2. Prevention and management of bleeding

Since patients with MHVs receive lifelong VKA, strategies to prevent bleeding need to be implemented. Proton pump inhibitors reduce the risk of upper gastrointestinal bleeding by approximately 40% in patients taking VKAs[825,839,840] and should therefore be prescribed to patients with MHVs, particularly in those with additional bleeding risk factors (e.g. elderly, antiplatelet agent co-administration, chronic use of non-steroidal anti-inflammatory drugs, high INR, or alcohol abuse). Randomized controlled trials and a meta-analysis did not demonstrate a benefit of oral vitamin K1 supplementation in addition to temporary VKA cessation in non-bleeding patients with a supratherapeutic INR (4.5–10.0), with a trend toward reduced safety, which may be relevant for MHV patients.[841,842] For non-bleeding patients with an INR of >10.0, oral vitamin K1 (2.0–3.0 mg) should be administered, avoiding overcorrection.[841,843]

In cases of uncontrolled life-threatening or other major bleeding,[844] VKA use must be interrupted and reversal with non-activated four-factor prothrombin complex concentrates is preferred over fresh frozen plasma, because of higher safety and effectiveness.[845–848] A reduced starting dose (12.5 rather than 25 IU/kg) in patients with more thrombogenic MHVs may be considered.[849] In addition, vitamin K1 should be administered to reverse the effect of VKA. Intravenous route corrects INR ~4 h faster than oral administration,[850] with no differences at 24 h and an unknown clinical impact. VKA should be restarted as soon as major bleeding is controlled.

14.3.1.3. Management of anticoagulation therapy before and after non-cardiac invasive procedures

In patients with an MHV, VKA treatment should not be interrupted for: minor or minimally invasive procedures on the skin or eyes (including cataract with topical anaesthesia); dental cleaning, treatment of caries, and dental extractions; pacemaker implantation; cardiac catheterization; and endoscopic procedures (*Recommendation Table 15*; *Table 11*).[851–856] Topical antifibrinolytic or haemostatic agents may improve local haemostasis.[853]

In patients with an MHV and high thromboembolic risk (*Recommendation Table 16*; *Table 11*) undergoing non-cardiac, elective major invasive procedures with high risk of bleeding (see Supplementary data online, *Table S6*), VKA treatment must be interrupted at least 4 days before the procedure, bridging with LMWH should be started as soon as the INR reaches a subtherapeutic value, and the INR should be <1.5 on the day of surgery.[816,857,858] Measuring anti-Xa activity at peak and trough may be appropriate to manage LMWH dosing in selected patients, such as those with severe obesity or underweight.[859] In cases of urgent, major invasive procedures, four-factor prothrombin complex concentrate should be administrated to timely correct the INR for the intervention, if needed. For the management of antithrombotic drugs in patients undergoing major cardiac surgery, please refer to recent EACTS Guidelines.[860]

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Recommendation Table 15 — Recommendations for the management of antithrombotic therapy in patients with a mechanical heart valve undergoing elective non-cardiac surgery or invasive procedures

Recommendations	Class[a]	Level[b]
Continuing VKA treatment is recommended in patients with an MHV for minor or minimally invasive interventions[c] associated with no or minimal bleeding.[851–856]	I	A
It is recommended to discontinue VKA at least 4 days before major non-cardiac elective surgery, aiming for an INR <1.5, and to resume VKA treatment within 24 h after surgery, or as soon as considered safe.[816,857,858]	I	B
VKA interruption and resumption with bridging[d] should be considered in patients with an MHV and thromboembolic risk factors[e] undergoing major NCS.[816,857,858]	IIa	B
Interruption (3–4 days before surgery) and resumption of VKA without bridging may be considered to reduce bleeding in patients with new-generation aortic MHVs and no other thromboembolic risk factors[e] undergoing major NCS or invasive procedures.[816,857,858,861–864]	IIb	B

AF, atrial fibrillation; h, hour; INR, international normalized ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; MS, mitral stenosis; NCS, non-cardiac surgery; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Skin; minor eye surgery including cataract; dental cleaning, treatment of caries, and dental extractions; pacemaker or device implantation; diagnostic cardiac catheterization; gastroscopic, colonoscopic, bronchoscopic, or genitourinary diagnostic or therapeutic procedures considered at low bleeding risk.
[d]Bridging needs to be started as soon as INR reaches a subtherapeutic value and on the first post-operative day or as soon as considered safe.
[e]MHV in mitral or tricuspid position, older MHV generations in any position, inherited or acquired hypercoagulable state, LV dysfunction (LVEF <35%), AF with significant MS, recent (<12 months) major thrombotic event (i.e. cardioembolic stroke, deep vein thrombosis, pulmonary embolism).

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Table 11 Peri-operative management of antithrombotic treatment in patients with a mechanical heart valve undergoing non-cardiac surgery based on type of procedure and underlying risk

		Minimally invasive procedures[a]		Major NCS or invasive procedures[a]	
		Pre-procedure	Post-procedure	Pre-procedure	Post-procedure
Low thromboembolic risk					
New-generation aortic MHV and no additional risk factors[b]	**OAC**	No interruption of VKA	Continue VKA	Interrupt VKA at least 3–4 days prior to procedure with target INR <1.5 on the day of surgery	Resume VKA as soon as feasible, within 24 h
	Bridging	—	—	No bridging may be considered	No bridging may be considered, unless unable to administer OAC
	Supporting measures	—	Topical antifibrinolytic or haemostatic agents may be considered to improve local haemostasis	—	Mechanical and pharmacological VTE prophylaxis, if indicated
Moderate-to-high thromboembolic risk					
MHV in mitral or tricuspid position or other thromboembolic risk factors[b]	**OAC**	No interruption of VKA	Continue VKA	Interrupt VKA at least 4 days prior to procedure with target INR <1.5 the day of the procedure	Resume VKA within 24 h
	Bridging	—	—	Bridging with LMWH or UFH if CKD stage IV or V, starting at INR below the therapeutic range	Bridging with UFH or LMWH post-operatively within 24 h
	Supporting measures	—	Topical antifibrinolytic or haemostatic agents may be considered to improve local haemostasis	—	Appropriate mechanical and pharmacological VTE prophylaxis

AF, atrial fibrillation; CKD, chronic kidney disease; h, hour; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; MS, mitral stenosis; NCS, non-cardiac surgery; OAC, oral anticoagulation; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]See Supplementary Table S6.
[b]Inherited or acquired hypercoagulable state, LV dysfunction (LVEF <35%), AF with significant MS, recent (<12 months) major thrombotic event (i.e. cardioembolic stroke, deep vein thrombosis, pulmonary embolism).

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For patients with an MHV and low cardioembolic risk (e.g. a new-generation MHV in the aortic position without additional risk factors) undergoing elective major NCS or invasive procedures, VKA interruption (3–4 days before surgery)[816,857,858,861–864] and resumption[861–863] within 24 h may be performed without bridging to reduce post-surgical bleeding without increasing the risk of thrombosis (see *Figure 18*).

14.3.2. Biological heart valves

The management of antithrombotic treatment after BHV implantation or valve repair is summarized in *Recommendation Table 16* and *Figure 19*.

14.3.2.1. Patients with a surgical biological heart valve and no indication for oral anticoagulation

The optimal antithrombotic strategy early after surgical implantation of an aortic BHV remains controversial due to the lack of high-quality evidence. Multiple observational studies support the short-term use of VKAs to reduce the risk of thromboembolism,[865,866] while data on DOACs are missing. A small RCT and a meta-analysis found that VKA treatment for 3 months significantly increased major bleeding compared with low-dose ASA, without reducing mortality or thromboembolic events, but statistical power was low.[867,868] Therefore, both strategies (OAC or ASA) are reasonable within 3 months of surgical aortic BHV implantation. In the absence of randomized evidence, patients undergoing mitral or tricuspid BHV implantation should receive OAC for at least 3 months due to the increased risk of AF and thromboembolisms.

14.3.2.2. Patients with a transcatheter heart valve and no indication for oral anticoagulation

Based on evidence from RCTs, lifelong low-dose ASA is the recommended antithrombotic treatment after TAVI in patients without OAC indication. In the Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation (POPular TAVI) trial (cohort A), the incidence of bleeding and the composite of bleeding or thromboembolic events were both reduced with ASA compared with DAPT at 1 year.[869] One RCT [Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortIc vaLve rEplacement (TAVR) to Optimize clinical outcomes, GALILEO], which investigated a systematic

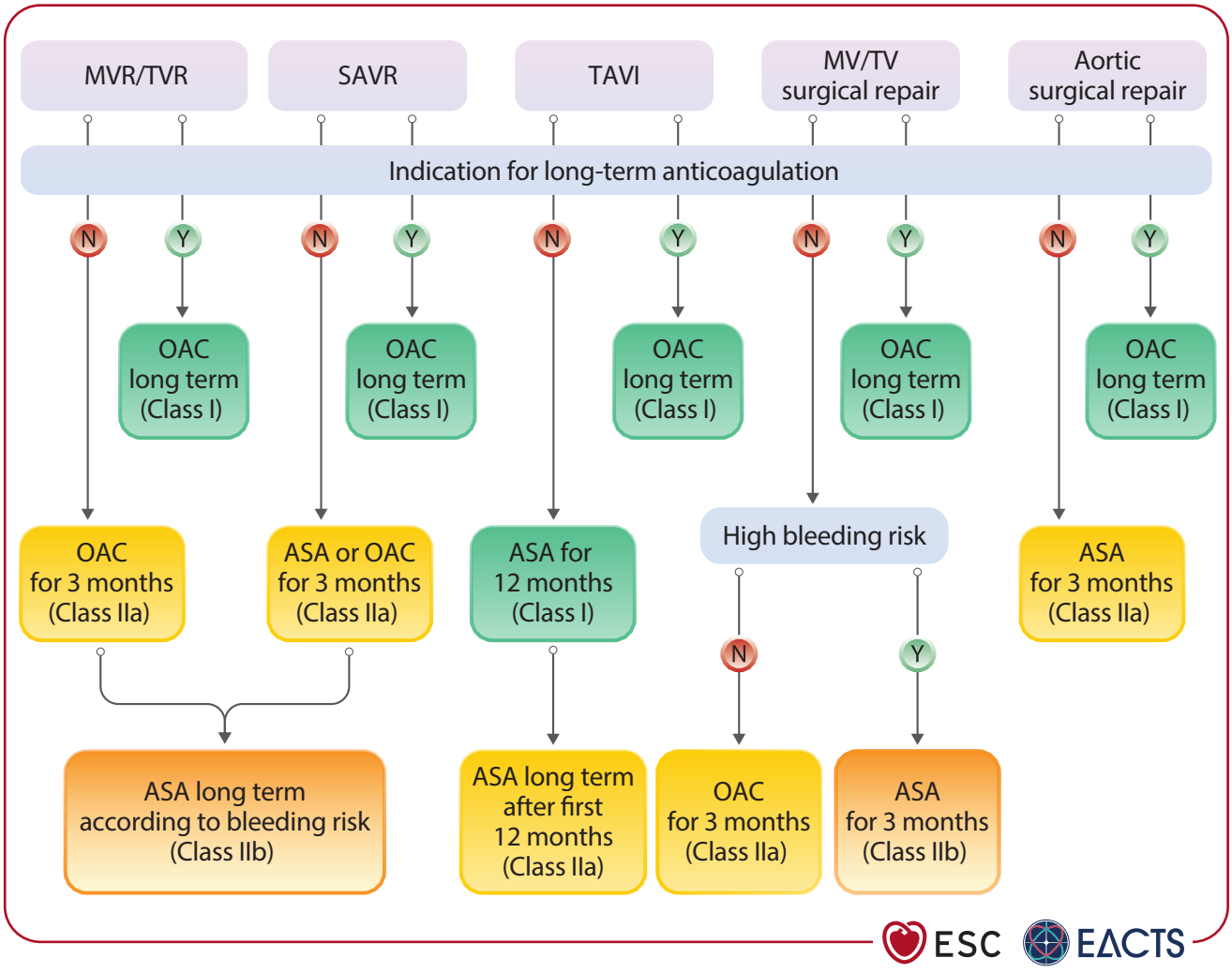
MVR/TVR
SAVR
TAVI
MV/TV surgical repair
Aortic surgical repair
Indication for long-term anticoagulation
N
Y
OAC long term (Class I)
OAC for 3 months (Class IIa)
ASA or OAC for 3 months (Class IIa)
ASA for 12 months (Class I)
High bleeding risk
ASA for 3 months (Class IIa)
ASA long term according to bleeding risk (Class IIb)
ASA long term after first 12 months (Class IIa)
OAC for 3 months (Class IIa)
ASA for 3 months (Class IIb)
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Figure 19 Antithrombotic therapy following biological heart valve implantation or surgical valve repair. ASA, acetylsalicylic acid; MV, mitral valve; MVR, mitral valve replacement; OAC, oral anticoagulation; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TV, tricuspid valve; TVR, tricuspid valve replacement.

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antithrombotic strategy of rivaroxaban (10 mg/day) in combination with low-dose ASA compared with DAPT with clopidogrel for the first 3 months, was halted prematurely due to an increased risk of death or thromboembolic complications, and an increased risk of bleeding in the rivaroxaban/ASA group.[870] The systematic use of DOACs after TAVI in patients without indication for OAC is therefore not recommended. Data on antithrombotic management after implantation of transcatheter mitral BHVs or tricuspid BHVs are limited. Vitamin K antagonist treatment for ≥3 months is commonly prescribed, while DOACs may represent an alternative allowing for earlier discharge and a lower risk of short-term bleeding complications (median follow-up, 4.7 months).[871]

For patients without baseline OAC undergoing mitral or tricuspid transcatheter valve implantation, OAC (either with DOAC or VKA) is initiated and usually pursued for at least 6 months or indefinitely (in particular after valve implantation in the tricuspid position), while patients undergoing TEER usually receive single long-term antiplatelet therapy with ASA.

14.3.2.3. Patients with a surgical biological heart valve and an indication for oral anticoagulation

Lifelong OAC is recommended for patients with surgical BHVs with other indications for OAC. The evidence supports the use of DOACs in preference to VKAs in patients with AF, even during the early post-operative period.[872–877] A previously existing therapy with a DOAC may be continued after BHV implantation and should be re-started, as soon as considered surgically safe, usually within 2–3 days of surgery.[860]

14.3.2.4. Patients with a transcatheter biological heart valve and an indication for oral anticoagulation

In the POPular TAVI trial (cohort B), the incidence of bleeding over a period of 1 month or 1 year was lower with OAC than with OAC plus clopidogrel.[878] Oral anticoagulation alone was non-inferior to OAC plus clopidogrel with respect to ischaemic events, but the non-inferiority margin was large. In Edoxaban vs Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation (ENVISAGE-TAVI-AF),[879] edoxaban was non-inferior to VKA regarding the composite primary endpoint (death from any cause, myocardial infarction, ischaemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding), but the incidence of major bleeding was higher with edoxaban than with VKA. The Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) trial[880] showed that apixaban was not superior to VKA after TAVI when there was a pre-existing indication for OAC, and there was a signal of higher non-cardiovascular mortality with apixaban. Therefore, no definitive recommendation can be made concerning the use of VKAs vs DOACs in patients who have undergone TAVI with a pre-existing indication for OAC.

Antithrombotic therapy after transcatheter MV or TV implantation remains empirical because data are limited. A high proportion of patients are already under OAC because of AF (almost 50% of the population with MR and 80%–90% of the candidates for TR treatment). Common practice is to continue the pre-existing anticoagulation regimen. Vitamin K antagonists and DOACs have been used in this setting with or without combination with ASA.[871] However, the high bleeding risk of this usually elderly population needs to be taken into consideration.

Recommendation Table 16 — Recommendations for the management of antithrombotic therapy in patients with a biological heart valve or valve repair

Recommendations	Class[a]	Level[b]
Surgical biological heart valve without indication for oral anticoagulation		
Low-dose ASA (75–100 mg/day) or OAC using a VKA should be considered for the first 3 months after surgical implantation of an aortic BHV in patients without clear indication for OAC.[865,866]	IIa	B
A VKA should be considered for the first 3 months after surgical implantation of a mitral or tricuspid BHV in patients without clear indication for OAC.[867,868]	IIa	B
Lifelong low-dose ASA (75–100 mg/day) may be considered 3 months after surgical implantation of an aortic or mitral BHV in patients without clear indication for OAC.	IIb	C
Transcatheter aortic valve implantation without indication for oral anticoagulation		
Low-dose ASA (75–100 mg/day) is recommended for 12 months after TAVI in patients without indication for OAC.[869,880–883]	I	A
Long-term (after the first 12 months) low-dose ASA (75–100 mg/day) should be considered after TAVI in patients without clear indication for OAC.	IIa	C
DAPT is not recommended to prevent thrombosis after TAVI, unless there is a clear indication.[881]	III	B
Routine use of OAC is not recommended after TAVI in patients without baseline indication.[869,880]	III	A
Surgical repair without indication for oral anticoagulation		
OAC, with either VKAs or DOACs, should be considered during the first 3 months after surgical MV or TV repair.[884–888]	IIa	B
Low-dose ASA (75–100 mg/day) should be considered for the first 3 months after surgical AV repair in patients without indication for OAC.	IIa	C
Low-dose ASA (75–100 mg/day) may be considered after surgical MV or TV repair in preference to OAC in patients without clear indication for OAC and at high bleeding risk.[884–888]	IIb	B
Surgical biological heart valve with indication for oral anticoagulation		
OAC continuation is recommended in patients with a clear indication for OAC undergoing surgical BHV implantation.[877,889,890]	I	B
DOACs should be considered over VKAs after 3 months following surgical implantation of a BHV in patients with AF.[872–874,876,891]	IIa	B
DOAC continuation may be considered after surgical BHV implantation in patients with an indication for DOAC.[877,889,890]	IIb	B

Continued

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Transcatheter biological heart valve with indication for oral anticoagulation		
OAC is recommended for TAVI patients who have other indications for OAC.[879,892–894]	I	B
Surgical repair with indication for oral anticoagulation and/or antiplatelet therapy		
Continuation of OAC or antiplatelet therapy should be considered after surgical valve repair in patients with a clear indication for an antithrombotic therapy.[890]	IIa	B

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AF, atrial fibrillation; ASA, acetylsalicylic acid; AV, aortic valve; BHV, biological heart valve; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; MV, mitral valve; OAC, oral anticoagulation; TAVI, transcatheter aortic valve implantation; TV, tricuspid valve; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

14.4. Management of prosthetic valve dysfunction and complications

Prosthetic valve dysfunction can occur due to intrinsic permanent changes to the prosthetic valve (defined as SVD) or non-structural valve dysfunction resulting from any abnormality not intrinsic to the prosthetic valve itself. Valve thrombosis and endocarditis are considered separate entities due to their specific presentation and management, but may both result in SVD.

14.4.1. Structural valve deterioration

Structural valve deterioration has been defined by several consensus documents[812,895,896] and includes wear and tear, leaflet disruption, leaflet fibrosis or calcification, and stent or strut fracture or deformation. BHV (transcatheter or surgical) SVD is more frequent than MHV SVD. The incidence of SVD may be underestimated by the simple analysis of patients with valve-related deaths or those undergoing reintervention. To ensure timely diagnosis, serial measurement should be performed and compared with the TTE performed at discharge, or within 1–3 months after valve implantation.

The criteria for haemodynamic deterioration associated with aortic and mitral SVD can be found in *Table 12*.[895,896] The diagnosis of moderate or severe haemodynamic deterioration should prompt referral to an experienced Heart Valve Centre for evaluation and treatment, and to exclude all causes of non-structural valve dysfunction, particularly PVL or PPM, as well as thrombosis and endocarditis. This step requires the use of advanced imaging techniques (TOE, CCT, and/or PET-CT) to document SVD-related morphological changes and elucidate its mechanism. Structural valve deterioration associated with corresponding clinical criteria (e.g. new onset or worsening of symptoms, LV or RV dilation/dysfunction, or PH) indicates BHV failure with potential need for reintervention. Decisions about the treatment modality (redo surgery or transcatheter valve-in-valve implantation) should be made within the interdisciplinary Heart Team, depending on re-operation risk and anatomical considerations,[445,897] including the risk of coronary obstruction,[144,442,446,461] as well as prosthesis type and size.[898–900] When considering a valve-in-valve procedure for a degenerated aortic BHV, the possibility of creating a PPM in small valves should be anticipated and may impact intervention or valve selection.[448]

Given the larger sizes of BHVs in mitral or tricuspid positions, transfemoral/transseptal valve-in-valve implantation represents an attractive alternative to redo open surgery.[570,900–903] In the case of mitral valve-in-valve implantation the risk of LVOT obstruction, although

Table 12 Criteria for the diagnosis of moderate or severe aortic and mitral haemodynamic valve deterioration

	Moderate	Severe
Aortic BHV SVD or non-structural valve dysfunction (except PVL or PPM),[a] thrombosis, or endocarditis	Increase in mean transvalvular gradient ≥10 mmHg resulting in mean gradient ≥20 mmHg	Increase in mean transvalvular gradient ≥20 mmHg resulting in mean gradient ≥30 mmHg
	AND	**AND**
	Decrease in EOA ≥0.3 cm^2 or ≥25%, and/or decrease in DVI ≥0.1 or ≥20%, compared with echocardiographic assessment performed 1–3 months post-procedure	Decrease in EOA ≥0.6 cm^2 or ≥50%, and/or decrease in DVI ≥0.2 or ≥40%, compared with echocardiographic assessment performed 1–3 months post-procedure
	OR	***OR***
	New occurrence or increase of ≥1 grade of intraprosthetic AR resulting in ≥ moderate AR	New occurrence or increase of ≥2 grades of intraprosthetic AR resulting in ≥ moderate-to-severe AR
Mitral BHV SVD or non-structural valve dysfunction (except PVL or PPM),[b] thrombosis, or endocarditis	Increase in DVI ≥0.4 or ≥20%, resulting in DVI ≥2.2, or decrease in EOA ≥0.5 cm^2 or ≥25%, resulting in EOA <1.5 cm^2, usually associated with increase of transmitral gradient ≥5 mmHg	Increase in DVI ≥0.8 or ≥40%, resulting in DVI ≥2.7, or decrease in EOA ≥1.0 cm^2 or ≥50%, resulting in EOA <1 cm^2, usually associated with increase of transmitral gradient ≥10 mmHg
	OR	***OR***
	New occurrence or increase of ≥1 grade of intraprosthetic MR resulting in ≥moderate MR	New occurrence or increase of ≥2 grades of intraprosthetic MR resulting in ≥moderate-to-severe MR

Adapted from [895,896].
AR, aortic regurgitation; AV, aortic valve; BHV, biological heart valve; DVI, Doppler velocity index; EOA, effective orifice area; MR, mitral regurgitation; PPM, prosthesis–patient mismatch; PVL, paravalvular leak; SVD, structural valve deterioration.
[a]Obstruction by pannus; dilatation of the aortic root after stentless BHV; or AV-sparing operations.
[b]Leaflet entrapment by pannus, chordae, or suture.

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infrequent, should be carefully ruled out, especially in patients with small and hypertrophic ventricles.[904]

14.4.2. Non-structural valve dysfunction

14.4.2.1. Prosthesis–patient mismatch

Prosthesis–patient mismatch should be prevented whenever possible after either transcatheter or surgical valve-replacement procedures (see *Section 8.5.1.2*). When occurring in the aortic position, severe PPM is associated with decreased quality of life, increased rate of rehospitalization and reintervention, and possible reduction in long-term survival, although findings are not consistent throughout all studies.[454,905–909] Moderate PPM is more common, but seems to have a limited impact on outcomes. The projected indexed EOA may be predicted prior to valve implantation to avoid severe PPM,[908] although this concept has been challenged.[910] Less is known about the prevalence and consequences of PPM in the mitral and tricuspid positions, and established definitions are lacking.

Prosthesis–patient mismatch is an infrequent indication for reintervention. However, reoperation should be considered in symptomatic patients with severe PPM, particularly if the patient is low risk.[394,437,438]

14.4.2.2. Paravalvular leak and haemolysis

The diagnosis of PVL requires systematic TOE, because TTE may be inconclusive. Haemolytic anaemia can often be detected in patients with prosthetic valves and is best assessed by measuring lactate dehydrogenase and haptoglobin serum levels, but rarely leads to symptoms. Intervention is needed if a PVL causes haemolysis requiring blood transfusions or symptoms, or if secondary to valve endocarditis. Transcatheter PVL closure is a valid alternative to surgery in the case of significant regurgitation or haemolysis, if feasible depending on the size and location of the leak, but requires specific expertise and planning. Care must be taken not to interfere with mechanical leaflet motion in MHV patients. Reported results for transcatheter PVL closure are inconsistent, with several patients returning with recurrent PVL and/or haemolysis.[911] When surgery or transcatheter intervention are contraindicated, medical therapy aims to counteract the effect of haemolysis (iron supplementation and erythropoietin) or reduce it (beta-blockers).[912]

14.4.3. Endocarditis

Antibiotic prophylaxis is recommended in all patients with a prosthetic valve (including transcatheter valve prostheses) and after valve repair using prosthetic material or with previous episode(s) of infective endocarditis, and should also be considered after transcatheter MV or TV repair.[5] It is recommended in such patients when undergoing dental extractions, oral surgery, or other procedures requiring manipulation of the gingival or peri-apical region of the teeth. Particular attention to dental and cutaneous hygiene, and strict aseptic measures during any invasive procedure, are also advised in this population. Additional details on endocarditis prophylaxis are mentioned in the *2023 ESC Guidelines for the management of endocarditis*.[5]

14.4.4. Valve thrombosis

Valve thrombosis occurs mainly in MHVs,[913,914] but can also be observed in BHVs.[915,916] The spectrum of BHV thrombosis ranges from incidental CCT findings, such as hypo-attenuated leaflet thickening (HALT) with or without reduced leaflet motion but normal gradients, to clinically apparent presentations with elevated gradients, symptoms of valve obstruction, or thromboembolic events.[917–919]

14.4.4.1. Hypo-attenuated leaflet thickening

Hypo-attenuated leaflet thickening is detected by CCT in 10%–30% of aortic BHVs depending on antithrombotic management, the definition of HALT, the timepoint of assessment, and the type of valve.[917,919–921] The significance and clinical implications of these findings with respect to thromboembolic risk and valve durability remain uncertain. Accordingly, routine use of CCT to detect HALT is not indicated.[918–920] In patients with relevant increases in gradients, in whom HALT and restricted leaflet motion is confirmed by CCT, elective use of DOACs or VKAs should be considered to resolve leaflet thrombosis.[918,921,922]

14.4.4.2. Clinically significant valve thrombosis

Obstructive valve thrombosis should be suspected in any patient with any type of prosthetic valve who presents with new-onset dyspnoea or HF symptoms, an embolic event, or an unexpected increase in transvalvular gradients. If TTE findings are uncertain, the diagnosis should be confirmed by TOE and/or CCT to distinguish between thrombus, pannus, and degeneration.[923–925] Cinefluoroscopy can detect impaired MHV leaflet motion and reduced opening angles.

Adequate anticoagulation must be promptly restored in all patients with MHV thrombosis and subtherapeutic INR. Although surgery remains the first-line option in critically ill patients, emergency valve replacement is associated with increased risk, whereas bleeding and systemic embolism are increased with fibrinolysis.[926–928] Slow, low-dose infusion appears to lower complication rates, while preserving thrombolytic success rates.[928–931a] It is recommended that the decision between surgery and fibrinolysis is taken within the Heart Team, and individualized by weighing clinical factors and local expertise (*Figure 20*).

Management of non-obstructive thrombosis or obstructive thrombosis of an MHV without pronounced HF symptoms depends mainly on the occurrence of a thromboembolic event and the size of the thrombus. Surgery should be considered for a large (>10 mm) non-obstructive prosthetic valve thrombus that is complicated by embolism or persists despite optimal OAC.[913,932,933]

Anticoagulation using a VKA is the first-line treatment for clinically relevant BHV thrombosis, unless urgent reintervention or fibrinolysis is required due to progressive acute HF or haemodynamic instability.[934–938] Because clinically relevant BHV thrombosis is associated with recurrence and may contribute to prosthetic degeneration, indefinite anticoagulation may be considered after a confirmed episode, but this strategy must be balanced against the risk of bleeding.[936,939]

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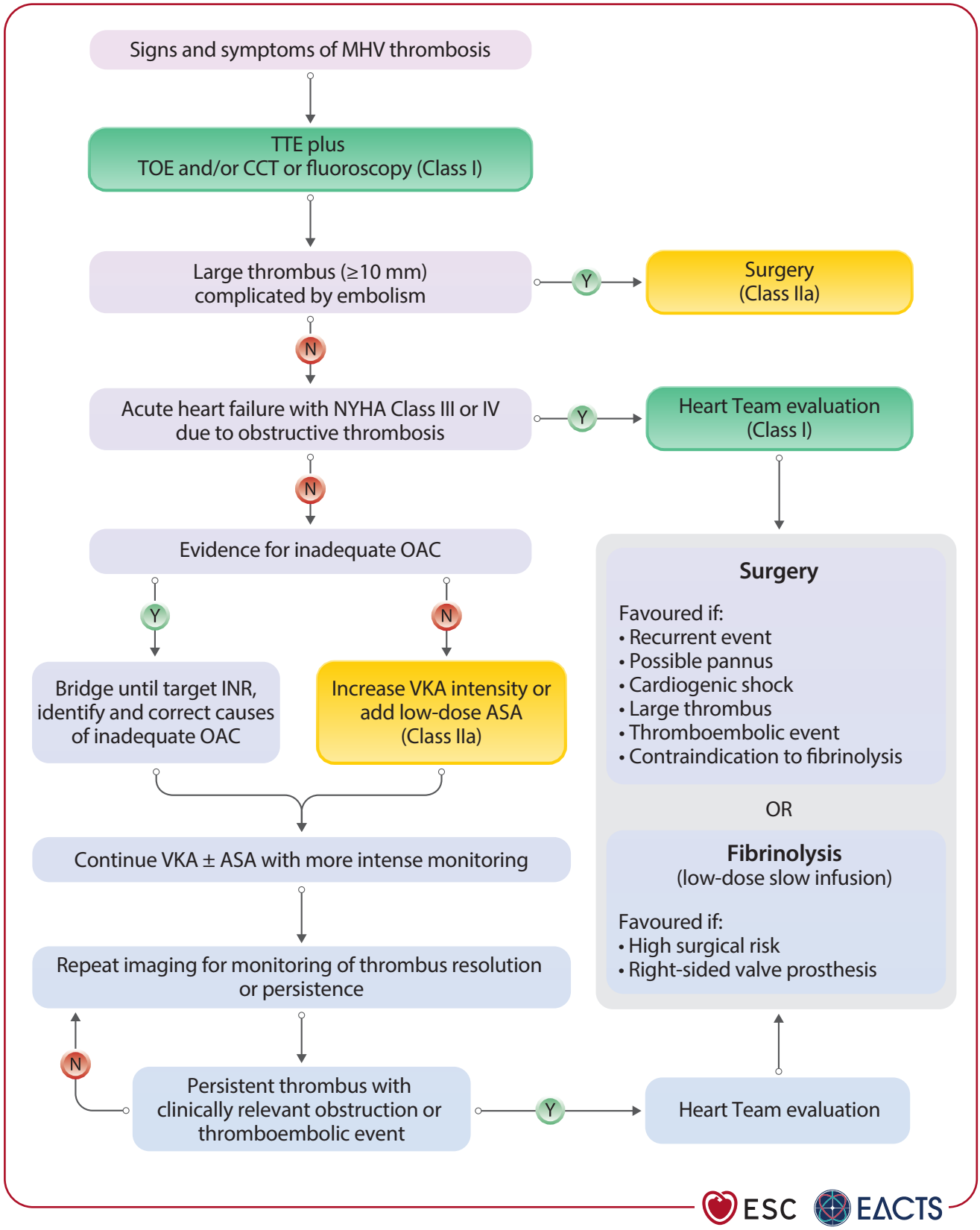

Figure 20 Management of left-sided obstructive and non-obstructive mechanical heart valve thrombosis. ASA, acetylsalicylic acid; CCT, cardiac computed tomography; INR, international normalized ratio; MHV, mechanical heart valve; NYHA, New York Heart Association; OAC, oral anticoagulation; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; VKA, vitamin K antagonist.

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Recommendation Table 17 — Recommendations for the management of prosthetic valve dysfunction (see also Supplementary data online, *Evidence Table 25*)

Recommendations	Class[a]	Level[b]
Haemolysis and paravalvular leak		
It is recommended that the decision between transcatheter or surgical closure of clinically significant PVLs is based on Heart Team evaluation, including patient risk, leak morphology, and local expertise.	I	C
Reoperation is recommended if a PVL is related to endocarditis, or causes haemolysis requiring repeated blood transfusion or leading to HF symptoms.	I	C
Transcatheter closure should be considered for suitable PVLs with clinically significant regurgitation and/or haemolysis.[940]	IIa	B
Mechanical heart valve failure		
Reoperation is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Biological heart valve failure		
Reintervention is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Transcatheter, transfemoral valve-in-valve implantation in the aortic position should be considered in patients with significant valve dysfunction who are at intermediate or high surgical risk, and have suitable anatomical and prosthesis features, as assessed by the Heart Team.[447,448,450,451,941]	IIa	B
Transcatheter transvenous mitral or tricuspid valve-in-valve implantation should be considered in patients with significant valve dysfunction at intermediate or high surgical risk, if the anatomy is suitable.[569,570,681,942–944]	IIa	B
Reoperation should be considered in asymptomatic patients with significant prosthetic dysfunction, if surgical risk is low.	IIa	C
Valve thrombosis		
TOE and/or 4D-CT are recommended in patients with suspected valve thrombosis to confirm the diagnosis.[914,918,923,925,945–948]	I	C
Mechanical heart valve thrombosis		
Heart Team evaluation is recommended in patients with acute HF (NYHA class III or IV) due to obstructive MHV thrombosis to determine appropriate management (repeat valve replacement or low-dose slow infusion fibrinolysis).[923,926–929,931,949–954]	I	B
Surgery should be considered for large (>10 mm) prosthetic thrombus complicated by embolism.[913,932,933]	IIa	C
Biological heart valve thrombosis		
OAC using VKA is recommended in BHV thrombosis before considering reintervention.[867,934–937,955,956]	I	B
OAC should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients at least until resolution.[918,920–922]	IIa	B

4D, four-dimensional; BHV, biological heart valve; CT, computed tomography; HF, heart failure; MHV, mechanical heart valve; NYHA, New York Heart Association; OAC, oral anticoagulation; PVL, paravalvular leak; TOE, transoesophageal echocardiography; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

15. Management during non-cardiac surgery

In patients with significant VHD who undergo NCS, the risk of peri-operative cardiovascular complications is increased and related to both the timing of the procedure (i.e. urgent vs non-urgent) and type of surgery (low, intermediate, or high risk), as well as patient-specific factors (type and severity of VHD, LV function, etc.).[194,957–959] Detailed recommendations related to NCS are available in the *2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery*.[960]

15.1. Pre-operative evaluation

Echocardiography should be performed in all patients with VHD requiring NCS. Patient- and surgery-specific factors, along with risk calculators, can be used to guide the treatment strategy. Determination of functional capacity is a pivotal step for pre-operative risk assessment, measured either by the ability to perform activities in daily life or by exercise testing. Screening for frailty using validated tools is advisable.[90] Decisions on pre- and peri-operative management, surveillance, and continuation of chronic cardiovascular medical treatment should be taken after multidisciplinary discussion involving cardiologists, surgeons, and cardiac anaesthesiologists, as well as the team who will be in charge of the NCS. Patients receiving OAC treatment should be managed as described in *Section 14*.

15.2. Specific valve lesions

15.2.1. Aortic stenosis

In patients with severe symptomatic AS, the treatment depends on the urgency and risk of NCS. If life-saving time-sensitive NCS is needed, it should be performed under careful haemodynamic monitoring avoiding rapid changes of volume status, with prompt treatment of arrhythmia regardless of AS severity. In cases of urgent high-risk NCS, TAVI or balloon aortic valvuloplasty should be considered in patients with critical AS prior to surgery, considering the risk of developing severe acute AR after

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balloon aortic valvuloplasty.[194,961] Urgent low- and intermediate-risk NCS can be performed relatively safely in patients with severe AS.[962]

Patients in whom NCS can be deferred (i.e. non-urgent NCS) should undergo pre-operative Heart Team evaluation to determine whether SAVR or TAVI is preferable. TAVI may be preferred to SAVR if faster recovery plays a role, particularly in elderly patients in whom complex or high-risk NCS is planned.[963] The treatment of asymptomatic patients with severe AS should be individualized (*Figure 21*).[964]

15.2.2. Mitral stenosis

Heart rate and fluid balance should be controlled to prevent pulmonary oedema during NCS and arterial vasodilators should be avoided. Non-cardiac surgery is safe in patients with an MVA of >1.5 cm^2, and in asymptomatic patients with MVA ≤1.5 cm^2 and SPAP of <50 mmHg. Symptomatic patients or those with SPAP of >50 mmHg should undergo PMC or other appropriate valve intervention before high-risk NCS, if possible.[965,966] Asymptomatic patients with MVA ≤1.5 cm^2 can undergo low-to-moderate-risk NCS under careful monitoring, especially if PMC is unsuitable. Multidisciplinary management is advised for patients with significant MS who are ineligible for valve intervention.

15.2.3. Aortic and mitral regurgitation

Non-cardiac surgery can usually be performed safely in asymptomatic patients with severe MR or AR and preserved LV function. If NCS is urgent, patients should undergo surgery under strict haemodynamic monitoring, regardless of symptom status. In cases of elective (non-urgent) NCS in patients with severe ventricular SMR, medical therapy should be optimized. If symptoms persist and NCS is intermediate or high risk, TEER should be considered after Heart Team discussion based on clinical

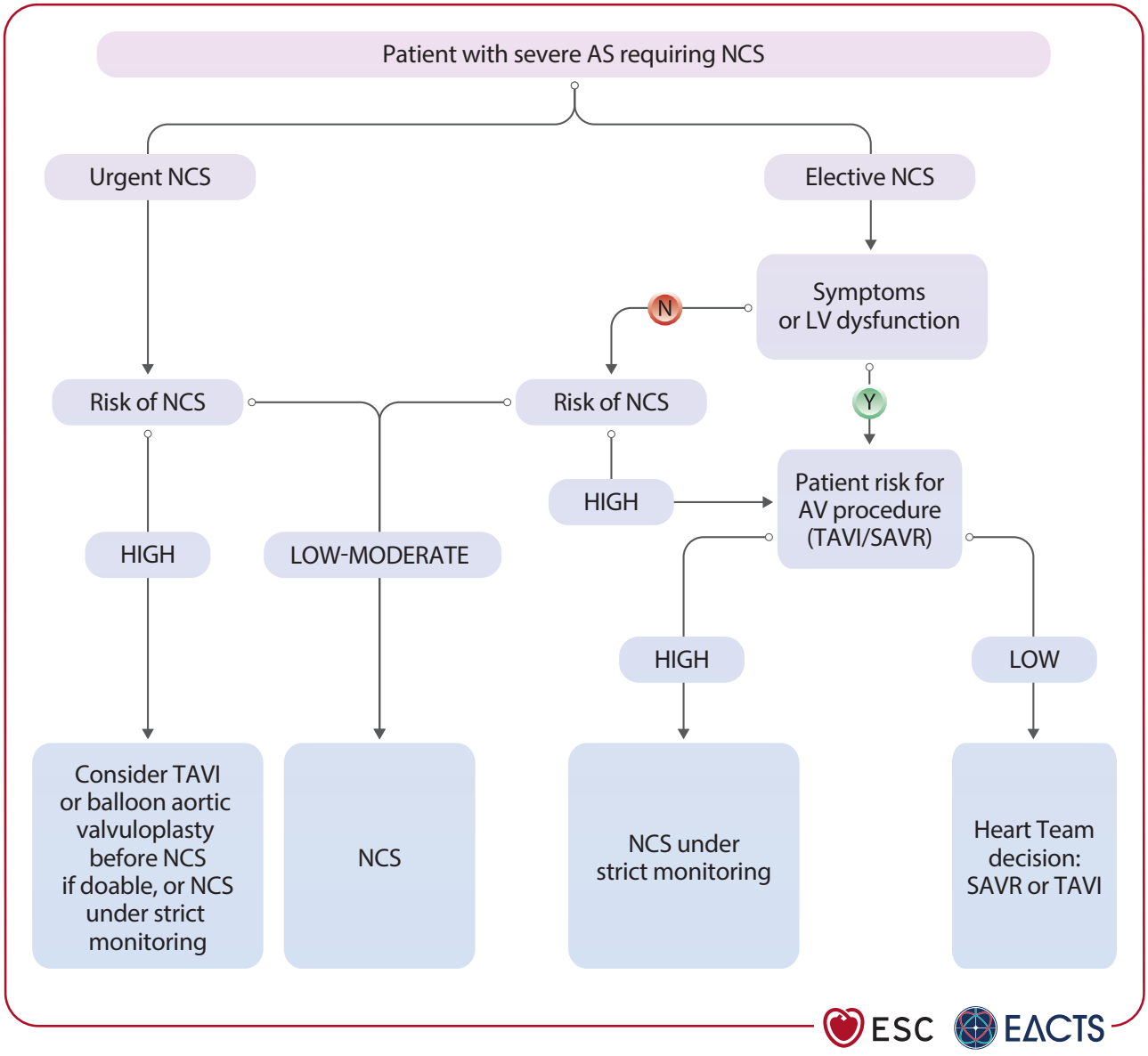

Figure 21 Management of non-cardiac surgery in patients with severe aortic stenosis. AS, aortic stenosis; AV, aortic valve; LV, left ventricular; NCS, non-cardiac surgery; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

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and anatomical selection criteria.[194,584] Valve treatment should be performed for patients with AR meeting the criteria for valve intervention before any elective intermediate- or high-risk NCS.[966,967]

15.3. Peri-operative monitoring

Heart rate control (particularly in MS) and careful fluid management (particularly in AS and MR with reduced LVEF) are needed throughout the procedure. The involvement of specialized cardiovascular anaesthesiologists should be considered in complex situations because TOE monitoring may be considered. Pulmonary artery catheterization is not routinely used.

16. Management of valvular heart disease during pregnancy

Specific ESC Guidelines on this topic are available (the *2025 ESC Guidelines on cardiovascular disease during pregnancy*) and should be consulted for further details.[968] Pregnancies in patients with VHD should be considered high risk and managed under the close supervision of a cardiologist and a multidisciplinary Pregnancy Heart Team. The importance of midwives and other specialized nursing personnel is increasingly recognized for high-quality direct patient interactions. Shared decision-making is especially important when addressing the cardiovascular risk of pregnancy and the benefit–risk ratios of therapeutic options and modes of delivery (*Figure 22*).

16.1. Management before pregnancy

Ideally, women should undergo a thorough physical examination by their general practitioner for VHD screening prior to pregnancy. A specialized evaluation including TTE should be performed by a cardiologist in the case of clinical suspicion.[968,969]

If VHD is diagnosed, pre-pregnancy counselling is imperative. Unplanned pregnancies in patients with VHD should be discouraged. Contraception methods should be recommended after discussion with the patient in the presence of a significant maternal and/or foetal risk. In patients contemplating pregnancy, the maternal risk should be assessed using the modified WHO classification and other scores such as the CARPREG or DEVI risk score (see Supplementary data online, *Table S7*).[970]

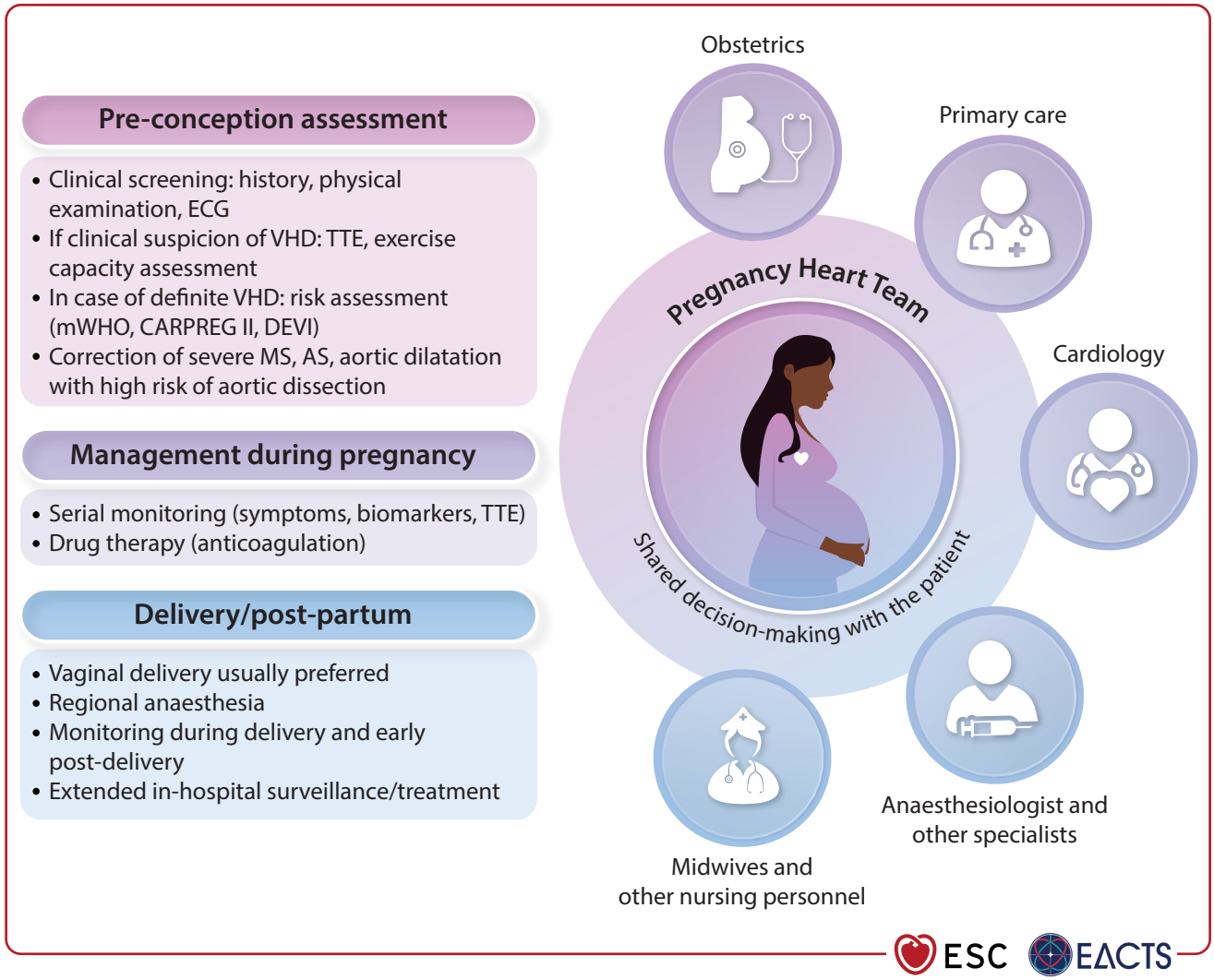
Pre-conception assessment
• Clinical screening: history, physical examination, ECG
• If clinical suspicion of VHD: TTE, exercise capacity assessment
• In case of definite VHD: risk assessment (mWHO, CARPREG II, DEVI)
• Correction of severe MS, AS, aortic dilatation with high risk of aortic dissection
Management during pregnancy
• Serial monitoring (symptoms, biomarkers, TTE)
• Drug therapy (anticoagulation)
Delivery/post-partum
• Vaginal delivery usually preferred
• Regional anaesthesia
• Monitoring during delivery and early post-delivery
• Extended in-hospital surveillance/treatment
Obstetrics
Primary care
Pregnancy Heart Team
Cardiology
Shared decision-making with the patient
Anaesthesiologist and other specialists
Midwives and other nursing personnel
ESC
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Figure 22 The Pregnancy Heart Team model of care. AS, aortic stenosis; ECG, electrocardiogram; MS, mitral stenosis; TTE, transthoracic echocardiography; VHD, valvular heart disease.

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Before recommending pregnancy, the following conditions need to be corrected:

- MS with MVA <1.5 cm^2, even when asymptomatic.[971]
- Severe AS with symptoms, or abnormal exercise test, or LV systolic dysfunction.[972]
- Heritable aortic disorders and high risk of aortic dissection: prophylactic aortic repair is recommended prior to pregnancy in women with Marfan syndrome and an aortic diameter of >45 mm, and may be considered in women with an aortic diameter between 40 and 45 mm when risk factors for dissection exist.[973] Aneurysmal dilation in women with BAV should be corrected when the aortic diameter is ≥50 mm.[974] Close follow-up in dedicated units and beta-blocker therapy during pregnancy and post-partum are recommended unless contraindicated, although strong evidence is only available for Marfan syndrome.

Valvular regurgitant lesions are generally well tolerated during pregnancy. Prophylactic intervention is therefore not recommended in the absence of class I or IIa indications.

The first therapeutic option for MS in a woman considering pregnancy should be PMC. When implantation of a prosthetic valve is necessary, BHVs are recommended, although early SVD remains a serious concern.[975] Mechanical heart valves must be avoided due to the high risk of maternal and foetal complications linked to the potential teratogenic effects of VKAs, as well as the increased risk of bleeding.[976] The Ross procedure may be considered for the treatment of AV disease at centres with expertise.

16.2. Management during pregnancy

16.2.1. Patients with native valve disease

Pregnancy can worsen the clinical course of left-sided stenotic valvular lesions because increased cardiac output causes an increment of transvalvular gradient of ~50%, mainly between the first and second trimesters. Regurgitant lesions are less likely to cause complications, except in high-risk cases (LV systolic dysfunction, PH, and cardiac events before pregnancy).[977]

Mild MS is generally well tolerated.[978] Heart failure occurs in one-third of pregnant women with an MVA of <1.5 cm^2 and in one-half of those with an MVA of <1.0 cm^2, most often during the second trimester.[971] Percutaneous mitral commissurotomy should be considered if symptoms or SPAP of >50 mmHg persist despite optimal medical therapy (diuretics and beta-1-selective beta-blockers), preferably after the 20th week of pregnancy.

Regarding AS, pregnancy is generally well tolerated if prior exercise tolerance was normal, even in severe AS, while HF has been reported to occur in up to 25% of symptomatic patients.[972] In symptomatic patients despite medical therapy (i.e. diuretics), TAVI seems to be the preferred option in very selected patients, although evidence is lacking. Percutaneous balloon valvuloplasty may be an alternative option. Procedures should be performed in an experienced valve centre.[972,979,980]

Surgery under cardiopulmonary bypass is associated with a high rate of foetal loss and should be restricted to conditions that threaten the mother's life if transcatheter intervention is not possible or has failed.

Vaginal delivery is the first choice for the majority of patients. Caesarean section is preferred if there is an obstetric indication, and in the case of severe MS or AS, ascending aortic diameter of >45 mm, severe PH, or if delivery starts while the patient is being treated with OAC.

16.2.2. Patients with prosthetic valves

Pregnant patients with MHVs should be followed in a centre with corresponding expertise. In a cohort of 212 women with MHVs, valve thrombosis occurred in 10 (4.7%) pregnancies and haemorrhagic events occurred in 49 (23.1%).[976] Therapeutic OAC during pregnancy is essential to avoid thrombosis. The higher efficacy of VKAs compared with LMWH to prevent thrombosis must be balanced against increased foetal risks.[981]

In patients requiring ≤5 mg/day of warfarin, OAC with warfarin throughout pregnancy, changing to UFH before delivery, is advocated, in order to reduce the risk of thrombosis. In patients requiring higher doses, switching to dose-adjusted LMWH at least twice per day with strict anti-Xa monitoring during the first trimester is recommended to avoid the teratogenic effect of VKAs (for corresponding flowcharts see the *2025 ESC Guidelines for the management of cardiovascular diseases during pregnancy*[968]).

Lifetime management of women with a BHV considering pregnancy is central and transcatheter valve-in-valve implantation may be considered as a bridge to MHV implantation.[982]

17. Sex-specific considerations in patients with valvular heart disease

Although men and women are equally likely to experience VHD, sex-specific prevalence exists according to valve type and disease pathophysiology.[644,648,983] Women more frequently suffer from MV disease such as prolapse, RHD or TR, while men more often present with AS or AR, especially associated with BAV.[984] Men also suffer from endocarditis of any valve more frequently.[985]

Female sex is associated with higher mortality in the presence of various VHDs,[986] including early post-treatment,[987] and is included as a risk factor in surgical risk prediction tools such as the STS and EuroSCORE calculators. However, risk scores are often derived from populations including a majority of men.[988] In addition, risk prediction scores are susceptible to referral bias that results in a well-established higher risk of undertreatment or delayed treatment of VHD in women.[983,984,986]

17.1. Aortic valve disease

Female patients with severe AS present more often with shortness of breath, whereas males more frequently have angina, presumably due to the higher incidence of CAD.[989] The pathophysiology of AS seems to differ according to sex, with women having less calcium and more fibrosis.[990] Concentric ventricular hypertrophy and remodelling are also more frequently observed in women than in men, resulting in higher LVEF but smaller LV cavity and stroke volume.[991] Consequently, paradoxical low-flow, low-gradient constellations are frequent and may both contribute to the underdiagnosis of severe AS in women and delay an intervention.[992] The use of sex-specific thresholds to define flow limitation (<40 mL/m^2 for men and <32 mL/m^2 for women) has therefore been suggested,[292] and the use of CCT to quantify the calcium score should be performed in women with discordant echocardiographic parameters.[777]

Women are less likely to be referred to a cardiologist and undergo investigations. Surgical aortic valve replacement is performed less frequently in women, especially if echocardiographic parameters are discordant.[993] In patients presenting with severe

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AS and Class I indications for SAVR, a significantly higher proportion of men than women are referred for evaluation by a cardiac surgeon.[994,995]

Male patients derive a clearer benefit from SAVR compared with women, who have higher in-hospital and long-term mortality and morbidity,[987,996] possibly explained by more severe concentric hypertrophy[991] and a smaller aortic annulus predisposing to PPM.[997] Conversely, in a randomized trial (RHEIA) that compared TAVI with SAVR in 443 women with a mean age of 73 years, TAVI was superior in reducing the primary endpoint composed of death, stroke, or rehospitalization at 1 year, predominantly driven by a reduction in rehospitalization for valve- or procedure-related symptoms or worsening HF.[998] Several observational studies suggest that elderly women have lower mortality after TAVI,[999] even if the rates of major vascular complications and bleeding tend to be higher.[997]

Indexed cut-offs to indicate treatment of AR are validated, but only partially account for sex differences. Newer studies using echocardiographic volumes[1000] and CMR[1001] suggest that women may experience higher event rates at lower cut-offs compared with men, but this requires further investigation.

17.2. Mitral valve disease

Patients with RHD are often young women and have a high prevalence of major cardiovascular complications with far-reaching impacts on reproductive health and access to care.[282] Although women experience favourable outcomes compared with men when treated by percutaneous balloon valvuloplasty, access to these procedures is still limited in low-income countries.[662]

Fibroelastic disease with MV prolapse is also more frequent in women, and may be accompanied by morphological abnormalities of the MA associated with fibrosis of the papillary muscles or the inferobasal LV that may act as the substrate for sudden cardiac death, even in the absence of severe MR.[1002] Recent evidence has supported considering lower women-specific cut-offs for intervention with regard to LVESD (36 mm; indexed LVESD, 1.8 cm/m^2), while the LVEF cut-off was similar to men (58%), albeit with higher mortality.[548]

Ventricular SMR associated with low LVEF is more frequent in men with HF,[1003] while atrial SMR due to chronic AF and/or HFpEF affects more women (58% vs 42% male).[579]

Female sex is a risk factor for the development of MAC and was reported to account for 68% of the patients included in a large-scale transcatheter MV replacement in MAC registry.[1004] Furthermore, women present with a faster disease progression.[1005]

17.3. Tricuspid valve disease

Tricuspid regurgitation is more prevalent in women,[208] and female sex is associated with accelerated disease progression.[1006–1008] Hypotheses to explain these observations include the overall higher prevalence of HFpEF and AF in women.[1009] Women are usually diagnosed at an older age and the cause of TR is most frequently a consequence of left valvular disease or annular dilatation attributable to RA dilatation.[1010] No differences have been detected to date in terms of adverse events after surgery[1011] or transcatheter TV interventions.[1012,1013]

18. Key messages

Heart Team and Heart Valve Centre

- An integrated regional Heart Valve Network incorporating outpatient Heart Valve Clinics and specialist Heart Valve Centres allows optimal patient care.
- Heart Valve Centres should fulfil institutional and local statutory requirements, and strive for high procedural volume and excellent clinical outcomes.
- Heart Team recommendations should be based upon these guideline recommendations, relevant updated evidence, key medical considerations, and patient preferences.
- Core members of the Heart Team include the primary clinical cardiologist, cardiologists with subspecialty expertise in VHD, specialists in advanced cardiovascular imaging and peri-procedural imaging guidance, and surgeons and interventional cardiologists with training and expertise in valve interventions.
- A network approach that distinguishes between higher- and lower-volume centres is appropriate, with more complex procedures focused in the most experienced (i.e. upper quartile) centres. Information on the network organization should be communicated to patients, as well as referring cardiologists and general practitioners.

Aortic regurgitation

- Assessment of AR severity with TTE remains challenging and current cut-offs for intervention are mostly based on 2D measurements, although 3D echocardiography and CMR allow more accurate evaluation of LV volumes and LVEF.
- Mechanisms of AR may be closely related to the aortic diameters that should be measured accurately at all levels of the aortic root (annulus, sinuses, and sinotubular junction).
- Indication for operation is based on symptoms, LV volumes, LVEF, and aortic diameters. Although valve replacement remains the standard treatment, AV repair (or AV sparing when associated with root aneurysm) is being increasingly used to avoid prosthesis-related complications, especially in experienced centres.
- Current transcatheter options for AR are limited and applicable only in patients who are ineligible for surgery.

Aortic stenosis

- Diagnosis of severe AS requires integrative evaluation of pressure gradients (the most robust measurements), AVA, flow conditions, the extent of valve calcification, and LV function.
- Selection of the most appropriate mode of intervention should take into account clinical characteristics (age and estimated life expectancy, concomitant conditions), access and valve anatomy (particularly the feasibility of transfemoral TAVI and calcification patterns), and surgical risk, as well as repeat procedure options and risks (lifetime management).

Mitral regurgitation

- The echocardiographic diagnostic workup of patients with MR includes multiparametric assessment of MR severity, evaluation of

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MV anatomy (often with 3D TOE), identification of the mechanism (PMR, ventricular SMR, or atrial SMR), and evaluation of cardiac damage.
- Surgical MV repair is the preferred method of treatment in severe PMR. Transcatheter edge-to-edge repair is recommended in patients who are inoperable or high risk according to the Heart Team.
- Surgical MV repair is the procedure of choice for asymptomatic patients with primary MR and signs of cardiac damage, including moderate or more TR.
- In patients with ventricular SMR, GDMT (including CRT if indicated) is the initial and essential treatment step. In symptomatic patients without CAD needing revascularization, M-TEER is recommended. In patients with concomitant complex CAD and those not suitable for TEER, mitral surgery may be considered.
- In patients with atrial SMR, MV surgery, AF ablation if indicated, and LAAO should be considered after optimization of medical therapy. Transcatheter edge-to-edge repair may be considered in patients at high surgical risk.

Mitral stenosis

- Most patients with severe rheumatic MS and favourable valve anatomy should undergo PMC, which is the standard of care. Surgery is recommended for symptomatic patients with contraindications or unfavourable anatomical and clinical characteristics for PMC.
- Decision-making in patients with unfavourable anatomy should take into account local PMC experience.
- In selected patients with clinically severe degenerative MS and MAC, transcatheter intervention or surgery may improve symptoms.

Tricuspid regurgitation

- Concomitant TV repair is the preferred method for patients with left-sided valve pathology and associated moderate or severe TR.
- The use of risk scores for the assessment of RV and secondary organ dysfunction should be strongly encouraged in patients with isolated severe TV disease.
- In isolated severe TR without severe RV dysfunction, surgery should be performed at an early stage in patients at low operative risk.
- In isolated severe TR patients at increased surgical risk, tricuspid TEER or transcatheter replacement should be considered to improve quality of life and RV remodelling, in the absence of severe RV dysfunction or pre-capillary PH.

Tricuspid stenosis

- TS is a very rare manifestation of acquired VHD in high-income countries.
- TS is mainly associated with rheumatic valve disease, carcinoid syndrome, or enzymatic disorders such as Fabry's or Whipple's disease.
- Treatment of symptomatic TS mainly involves surgical TV replacement.

Multiple and mixed valvular heart disease

- Transvalvular gradients and velocities reflect the combined burden of regurgitation and stenosis in mixed aortic and mitral disease.
- Treatment decisions should be based on the assessment of symptom and functional status, cardiac damage, anatomical suitability, and the risk–benefit ratio of intervention and lifetime management considerations.
- Patients with mixed moderate AS and AR have similar detrimental outcomes compared with those with severe isolated AS.
- In transcatheter procedures, which allow a sequential approach, downstream lesions should be treated first to prevent potential haemodynamic deterioration and allow improvement of upstream lesions due to changing loading conditions and reverse remodelling.

Antithrombotic treatment in patients with a mechanical heart valve

- International normalized ratio therapeutic range should be balanced to the type and anatomical site of MHV, as well to the thrombotic risk profile of the individual patient.
- Patient training, self-monitoring, and education can increase INR stability and TTR.
- Minor or minimally invasive NCS procedures do not require VKA interruption in patients with an MHV.
- In patients with an MHV undergoing elective major NCS, bridging may be omitted if the thromboembolic risk is low.

Non-cardiac surgery

- The risk of peri-operative cardiovascular complications related to surgery and to patient-specific factors should be evaluated and communicated to the patient and surgical team.
- In patients with symptomatic severe AS requiring urgent high-risk NCS, BAV or TAVI should be considered prior to surgery. In patients planned for elective NCS, AV intervention is recommended prior to NCS.

Pregnancy

- In women with VHD, decisions regarding management before and during pregnancy should be taken after discussion by the multidisciplinary Pregnancy Heart Team. Unplanned pregnancies should be discouraged.
- The following conditions should be corrected prior to considering pregnancy:
  - clinically severe MS (MVA <1.5 cm^2), even when asymptomatic
  - severe symptomatic AS, or asymptomatic patients with impaired LV function or a pathological exercise test
  - heritable aortic disorders and high risk of aortic dissection.
- Vaginal delivery is the first choice for the majority of patients. Indications for Caesarean section include pre-term labour in patients on OAC, severe MS or AS, aggressive aortic pathology, acute intractable HF, and severe PH.
- Women with MHVs should be managed in expert centres.

19. Gaps in evidence

General aspects

- Patient-reported outcome measures are infrequently reported in VHD studies. Patient-reported outcome measure-oriented studies are required to improve quality of life and patient satisfaction.
- Methods to address underdiagnosis and undertreatment of VHD need to be identified and implemented.

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Heart Team and Heart Valve Centre

- Structured research is required to investigate the relationship between procedural volume and clinical outcomes, in order to define minimum annual thresholds for individual operators and institutions undertaking surgical and transcatheter valve interventions.
- There is a pressing need to ensure higher dispersion and adoption of interventions for VHD, especially in middle- and low-income countries.

Conditions associated with valvular heart disease

- CAD:
  - The prognostic value of functional assessment of stable, moderate coronary stenosis in VHD patients remains to be determined.
  - The optimal strategy (invasive vs non-invasive) for CAD assessment in specific VHD populations remains to be elucidated.
  - The optimal timing of PCI in patients with CAD undergoing TAVI is yet to be determined.
  - The benefit of complete coronary revascularization with CABG in patients with combined VHD and CAD requires further research.
- AF:
  - It is unclear which patients with chronic persistent AF and concomitant VHD are deemed to be suitable for rhythm control therapy.
  - The protective effect against stroke of OAC with VKA or DOACs in patients after surgical or transcatheter LAAO remains to be determined.
- Cardiogenic shock and acute HF:
  - The optimal treatment strategy in VHD patients presenting with cardiogenic shock and acute HF is unknown.

Aortic regurgitation

- Impact of early LV remodelling on prognosis in asymptomatic AR patients is unknown.
- Prognostic value of CMR-derived indices in asymptomatic patients needs to be determined.
- More data are required on long-term results of surgical AV repair for AR.
- More evidence is required on transcatheter treatment options for AR, in particular using dedicated devices.

Aortic stenosis

- Better understanding of the pathophysiology of AS is needed to propose innovative medical therapy.
- Further research is required on:
  - Refined prognostic markers to guide timing of intervention in asymptomatic patients.
  - The role of revascularization in patients with severe AS and asymptomatic concomitant CAD.
  - Further data on the long-term durability of transcatheter valves in comparison with surgical BHVs in younger patients.
  - The role of TAVI in patients with BAV AS and patients <70 years of age.
  - Results of intervention (valve or coronary) after TAVI or SAVR.
  - Determining the optimal lifetime management strategy for AS patients.

Mitral regurgitation

- The association between primary MR and ventricular arrhythmias requires more investigation, including the impact of intervention on ventricular arrhythmias.
- More data are required on the role of TEER in patients with advanced HF.
- Long-term results of TEER need to be further assessed, including the clinical relevance of transmitral gradients after treatment of both primary and secondary MR.
- Results of ongoing trials comparing MV surgery with TEER in non-high risk primary MR patients are awaited.
- Data on the mid- and long-term clinical impacts of transcatheter MV replacement are required.
- More data on the clinical impacts of surgical and transcatheter treatment of atrial SMR are required.

Mitral stenosis

- The potential role of TMVI using dedicated devices in high-risk patients is to be determined, particularly those with severe MAC.

Tricuspid regurgitation

- The long-term risks and benefits of concomitant TV surgery in patients with less than moderate TR and annular dilatation undergoing left-sided valve surgery need to be determined.
- Further investigations are required on the outcomes of TV intervention in asymptomatic patients with severe TR and RV dysfunction or significant dilation.
- The importance of addressing concomitant AF in patients with TR needs to be investigated.
- More data are required on the indications, timing, and long-term outcomes of TV repair and replacement for TV disease.
- Better understanding is required of the respective role of surgery vs transcatheter TV therapy for TR treatment.

Tricuspid stenosis

- The role of transcatheter TV replacement remains unexplored in patients with TS. The most efficient way to achieve ventricular pacing in patients after TV replacement needs to be investigated.

Multiple and mixed valvular heart disease

- Further evaluation of the impact on outcomes and indication for intervention, as well as timing and modalities of intervention, is required.

Prosthetic valves

- Further development of current prosthetic valve devices is required to address their main complications (e.g. improved tissue processing to reduce degeneration of bioprostheses or new mechanical valve designs to reduce risk of thrombosis).
- Antithrombotic drugs in MHV patients:
  - Whether UFH or LMWH should be preferred as bridging therapy after MHV implantation, as well as their timing and dosage, remains to be established.
  - For patients with MHV undergoing major NCS, the optimal postoperative management and bridging of VKA needs further investigation.
  - The role of pharmacogenomics for VKORC1, CYP2C9, and CYP4F2 in patients with highly variable INR, and low TTR or major vascular complications despite good adherence, should be further investigated.
  - More data on the risks and benefits of slow thrombolysis for valve thrombosis are required.

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Pregnancy

- More data are required on optimal management of anticoagulation in pregnant women with MHVs. Prospective studies comparing different antithrombotic regimens are lacking.

Non-cardiac surgery

- Clinical utility of scales for peri-operative risk evaluation needs to be determined.

Sex-specific considerations

- The development of sex-adjusted surgical risk prediction tools is required.
- Additional data are needed to validate sex-specific cut-offs indicating interventions.
- Further research is needed to investigate sex-related differences in the prognosis and treatment of specific valve diseases, especially TR.

20. 'What to do' and 'What not to do' messages from the Guidelines

Class I and Class III recommendations from throughout the guideline document are summarized in *Table 13*.

Table 13 'What to do' and 'what not to do'

Recommendations	Class[a]	Level[b]
Recommendations for the management of coronary artery disease in patients with valvular heart disease		
CCTA is recommended before valve intervention in patients with moderate or lower (≤50%) pre-test likelihood of obstructive CAD.	I	B
Invasive coronary angiography is recommended before valve intervention in patients with high and very high (>50%) pre-test likelihood of obstructive CAD.	I	C
Invasive coronary angiography is recommended in the evaluation of CAD in patients with severe ventricular SMR.	I	C
CABG is recommended in patients with a primary indication for valve surgery and coronary artery diameter stenosis ≥70%.	I	C
Recommendations for the management of atrial fibrillation in patients with native valvular heart disease		
DOACs are recommended for stroke prevention in preference to VKAs in patients with AF and AS, AR, or MR who are eligible for OAC.	I	A
Concomitant surgical ablation is recommended in patients undergoing MV surgery with AF suitable for a rhythm control strategy to prevent symptoms and recurrence of AF, according to an experienced team of electrophysiologists and arrhythmia surgeons.	I	A
Surgical closure of the LA appendage is recommended as an adjunct to OAC in patients with AF undergoing valve surgery to prevent cardioembolic stroke and systemic thromboembolism.	I	B
The use of DOACs is not recommended in patients with AF and rheumatic MS with an MVA ≤2.0 cm^2.	III	B
Recommendations on indications for surgery in severe aortic regurgitation		
AV surgery is recommended in symptomatic patients with severe AR regardless of LV function.	I	B
AV surgery is recommended in asymptomatic patients with severe AR and LVESD >50 mm or LVESDi >25 mm/m^2 [especially in patients with small body size (BSA <1.68 m^2)] or resting LVEF ≤50%.	I	B
Valve-sparing aortic root replacement is recommended in young patients with aortic root dilatation at experienced centres when durable results are expected.	I	B
AV surgery is recommended in symptomatic and asymptomatic patients with severe AR undergoing CABG or surgery of the ascending aorta.	I	C
Recommendations for intervention and mode of intervention in severe aortic stenosis		
Symptomatic patients with severe aortic stenosis		
Intervention is recommended in symptomatic patients with severe, high-gradient AS [mean gradient ≥40 mmHg, V_{max} ≥4.0 m/s, and AVA ≤1.0 cm^2 (or ≤0.6 cm^2/m^2 BSA)].	I	B
Intervention is recommended in symptomatic patients with low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) AS with reduced LVEF (<50%) after careful confirmation that AS is severe.	I	B
Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe AS and LVEF <50% without another cause.	I	B
Mode of intervention in patients with symptomatic severe aortic stenosis		
It is recommended that AV interventions are performed in Heart Valve Centres that report their local expertise and outcome data, have on-site interventional cardiology and cardiac surgical programmes, and a structured collaborative Heart Team.	I	C
It is recommended that the mode of intervention is based on Heart Team assessment of individual clinical, anatomical, and procedural characteristics, incorporating lifetime management considerations and estimated life expectancy.	I	C

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TAVI is recommended in patients ≥70 years of age with tricuspid AV stenosis, if the anatomy is suitable.	I	A
SAVR is recommended in patients <70 years of age, if the surgical risk is low.	I	B
SAVR or TAVI are recommended for all remaining candidates for an aortic BHV according to Heart Team assessment.	I	B
Concomitant aortic valve surgery at the time of coronary artery bypass grafting or ascending aorta surgery		
SAVR is recommended in symptomatic and asymptomatic patients with severe AS undergoing CABG or surgical intervention on the ascending aorta.	I	C
Recommendations for intervention in severe mitral regurgitation		
Primary mitral regurgitation		
MV repair is the recommended surgical technique to treat patients with severe PMR when the result is expected to be durable.	I	B
MV surgery is recommended in symptomatic patients with severe PMR considered operable by the Heart Team.	I	B
MV surgery is recommended in asymptomatic patients with severe PMR with LV dysfunction (LVESD ≥40 mm or LVESDi ≥20 mm/m^2 or LVEF ≤60%).	I	B
Surgical MV repair is recommended in low-risk asymptomatic patients with severe PMR without LV dysfunction (LVESD <40 mm, LVESDi <20 mm/m^2, and LVEF >60%) when a durable result is likely, if at least three of the following criteria are fulfilled: • AF • SPAP at rest >50 mmHg • LA dilatation (LAVI ≥60 mL/m^2 or LA diameter ≥55 mm) • concomitant TR ≥ moderate.	I	B
Ventricular secondary mitral regurgitation and concomitant coronary artery disease		
MV surgery is recommended in patients with severe ventricular SMR undergoing CABG.	I	B
Ventricular secondary mitral regurgitation without concomitant coronary artery disease		
TEER is recommended to reduce HF hospitalizations and improve quality of life in haemodynamically stable, symptomatic patients with impaired LVEF (<50%) and persistent severe ventricular SMR, despite optimized GDMT and CRT (if indicated), fulfilling specific clinical and echocardiographic criteria.	I	A
Recommendations for mitral stenosis		
Indications for mitral valve surgery and transcatheter intervention in clinically severe rheumatic and degenerative mitral stenosis		
PMC is recommended in symptomatic patients in the absence of unfavourable characteristics for PMC.	I	B
PMC is recommended in any symptomatic patients with a contraindication or a high risk for surgery.	I	C
MV surgery is recommended in symptomatic patients who are not suitable for PMC.	I	C
Recommendations for tricuspid regurgitation		
Indications for intervention in tricuspid regurgitation		
Careful evaluation of TR aetiology, stage of the disease (i.e. degree of TR severity, RV and LV dysfunction, and PH), patient operative risk, and likelihood of recovery by a multidisciplinary Heart Team is recommended in patients with severe TR prior to intervention.	I	C
Patients with left-sided valvular heart disease requiring tricuspid valve surgery		
Concomitant TV surgery is recommended in patients with severe primary or secondary TR.	I	B
Patients with severe tricuspid regurgitation (without left-sided valvular heart disease requiring surgery)		
TV surgery is recommended in symptomatic patients with severe primary TR without severe RV dysfunction or severe PH.	I	C
Recommendations on tricuspid stenosis		
Surgery is recommended in symptomatic patients with severe TS.	I	C
Surgery is recommended in patients with severe TS undergoing left-sided valve intervention.	I	C
Recommendations for surgery of concomitant left-sided valvular heart disease		
Concomitant aortic stenosis		
SAVR is recommended in patients with severe AS undergoing surgery for another valve.	I	C
Concomitant aortic regurgitation		
AV surgery is recommended in patients with severe AR undergoing surgery for another valve.	I	C
Concomitant mitral regurgitation		
MV surgery is recommended in patients with severe MR undergoing surgery for another valve.	I	C

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Recommendations on indications for intervention in patients with mixed moderate aortic stenosis and moderate aortic regurgitation		
Intervention is recommended in symptomatic patients with mixed moderate AV stenosis and moderate regurgitation, and a mean gradient ≥40 mmHg or V_{max} ≥4.0 m/s.	I	B
Intervention is recommended in asymptomatic patients with mixed moderate AV stenosis and moderate regurgitation with V_{max} ≥4.0 m/s, and LVEF <50% not attributable to other cardiac disease.	I	C
Recommendations for prosthetic valve selection		
Mechanical heart valves		
An MHV is recommended according to the desire of the informed patient and if there is no contraindication to long-term anticoagulation.	I	C
Biological heart valves		
A BHV is recommended according to the desire of the informed patient.	I	C
A BHV is recommended when an adequate quality of anticoagulation with VKA is unlikely, in patients at high bleeding risk, or with estimated short life expectancy.	I	C
Recommendations for the management of antithrombotic therapy in patients with a mechanical heart valve replacement		
Lifelong OAC with a VKA is recommended for all patients with MHVs to prevent thromboembolic complications.	I	A
INR self-monitoring and self-management are recommended over standard monitoring in selected, trained patients to improve efficacy.	I	A
It is recommended that INR targets are based on the type and position of the MHV, and the patient's risk factors and comorbidities.	I	A
Patient education is recommended to improve the quality of OAC.	I	A
Following cardiac surgery with MHV implantation, it is recommended to start UFH or LMWH bridging and VKA within 24 h, or as soon as considered safe.	I	B
DOACs and/or DAPT are not recommended to prevent thrombosis in patients with an MHV.	III	A
Recommendations for the management of antithrombotic therapy in patients with mechanical heart valves undergoing elective non-cardiac surgery or invasive procedures		
Continuing VKA treatment is recommended in patients with an MHV for minor or minimally invasive interventions associated with no or minimal bleeding.	I	A
It is recommended to discontinue VKA at least 4 days before major elective NCS, aiming for an INR <1.5, and to resume VKA treatment within 24 h after surgery, or as soon as considered safe.	I	B
Recommendations for the management of antithrombotic therapy in patients with a biological heart valve or valve repair		
Transcatheter aortic valve implantation without indication for oral anticoagulation		
Low-dose ASA (75–100 mg/day) is recommended for 12 months after TAVI in patients without indication for OAC.	I	A
DAPT is not recommended to prevent thrombosis after TAVI, unless there is a clear indication.	III	A
Routine use of OAC is not recommended after TAVI in patients without baseline indication.	III	A
Surgical biological heart valve with indication for oral anticoagulation		
OAC continuation is recommended in patients with a clear indication for OAC undergoing surgical BHV implantation.	I	B
Transcatheter biological heart valve with indication for oral anticoagulation		
OAC is recommended for TAVI patients who have other indications for OAC.	I	B
Recommendations on management of prosthetic valve dysfunction		
Haemolysis and paravalvular leak		
It is recommended that the decision between transcatheter or surgical closure of clinically significant PVLs is based on Heart Team evaluation, including patient risk, leak morphology, and local expertise.	I	C
Reoperation is recommended if a PVL is related to endocarditis, or causes haemolysis requiring repeated blood transfusion or leading to HF symptoms.	I	C
Mechanical heart valve failure		
Reoperation is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Biological heart valve failure		
Reintervention is recommended in symptomatic patients with significant valve dysfunction not attributable to valve thrombosis.	I	C
Valve thrombosis		
TOE and/or 4D-CT are recommended in patients with suspected valve thrombosis to confirm the diagnosis.	I	C

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Mechanical heart valve thrombosis		
Heart Team evaluation is recommended in patients with acute HF (NYHA class III or IV) due to obstructive MHV thrombosis to determine appropriate management (repeat valve replacement or low-dose slow infusion fibrinolysis).	I	B
Biological heart valve thrombosis		
OAC using VKA is recommended in BHV thrombosis before considering reintervention.	I	B

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4D, four-dimensional; AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; ASA, acetylsalicylic acid; AV, aortic valve; AVA, aortic valve area; BHV, biological heart valve; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCTA, coronary CT angiography; CRT, cardiac resynchronization therapy; CT, computed tomography; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulation; GDMT, guideline-directed medical therapy; h, hour; HF, heart failure; INR, international normalized ratio; LA, left atrium/left atrial; LAVI, left atrial volume index; LMWH, low-molecular-weight heparin; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter indexed to BSA; MHV, mechanical heart valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; MVA, mitral valve area; NCS, non-cardiac surgery; NYHA, New York Heart Association; OAC, oral anticoagulation; PH, pulmonary hypertension; PMC, percutaneous mitral commissurotomy; PMR, primary mitral regurgitation; PVL, paravalvular leak; RV, right ventricle/right ventricular; SAVR, surgical aortic valve replacement; SMR, secondary mitral regurgitation; SPAP, systolic pulmonary artery pressure; SVi, stroke volume index; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair; TOE, transoesophageal echocardiography; TR, tricuspid regurgitation; TS, tricuspid stenosis; TV, tricuspid valve; UFH, unfractionated heparin; VKA, vitamin K antagonist; V_{max}, peak transvalvular velocity.
[a]Class of recommendation.
[b]Level of evidence.

21. Evidence tables

Evidence tables are available at *European Heart Journal* online.

22. Data availability statement

No new data were generated or analysed in support of this research.

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24. Appendix

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